COMPARATIVE STUDY ON EFFECT OF NATURAL AND SYNTHETIC SUPERDISINTEGRANTS IN THE FORMULATION OF LEVOCETIRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS

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In partial fulfillment of the requirements
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MASTER OF PHARMACY

IN

BRANCH I - PHARMACEUTICS

Submitted by

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MAY 2018

CERTIFICATE

This is to certify that the dissertation entitled **"COMPARATIVE STUDY ON EFFECT OF NATURAL AND SYNTHETIC SUPERDISINTEGRANTS IN THE FORMULATION OF LEVOCETIRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS"** is a bonafide work done by **Ms.M.MUTHUMARI (Reg.No.261611304)** in the **DEPARTMENT OF PHARMACEUTICS, COLLEGE OF PHARMACY, MADURAI MEDICAL COLLEGE, MADURAI-625020,** in partial fulfilment of The Tamil Nadu Dr.M.G.R Medical University rules and regulations for award of Degree of **MASTER OF PHARMACY** (II year, Pharmaceutics) under my guidance and supervision during the academic year 2017-2018.

Name & Signature of Guide.

Name & Signature of Head of Dept.

Name & Signature of Dean/Principal.

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Place:

Date:

(M.MUTHUMARI)

DEDICATED
TO MY
FAMILY
MEMBERS
AND
WELL WISHERS

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CHAPTER – I

INTRODUCTION

INTRODUCTION

Among all the route of drug delivery system, drug delivery through the oral route is most common and preferred for both solid and liquid dosage forms. Solid dosage forms are more popular. Tablet is one of the preferred solid dosage form because of its dose, safest and economical **(Adchitre Vaishali B *et al.,* 2016).**

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia, Tablets are solid, flat or biconvex dishes, unit dosage form prepared by compressing a drug or a mixture of drugs with or without diluents. They vary in shape and differ greatly in size and weight depending on the amount of medical substances and the intended mode of administration. All the medicaments are available in the tablet form except where it is difficult to formulate or administer.

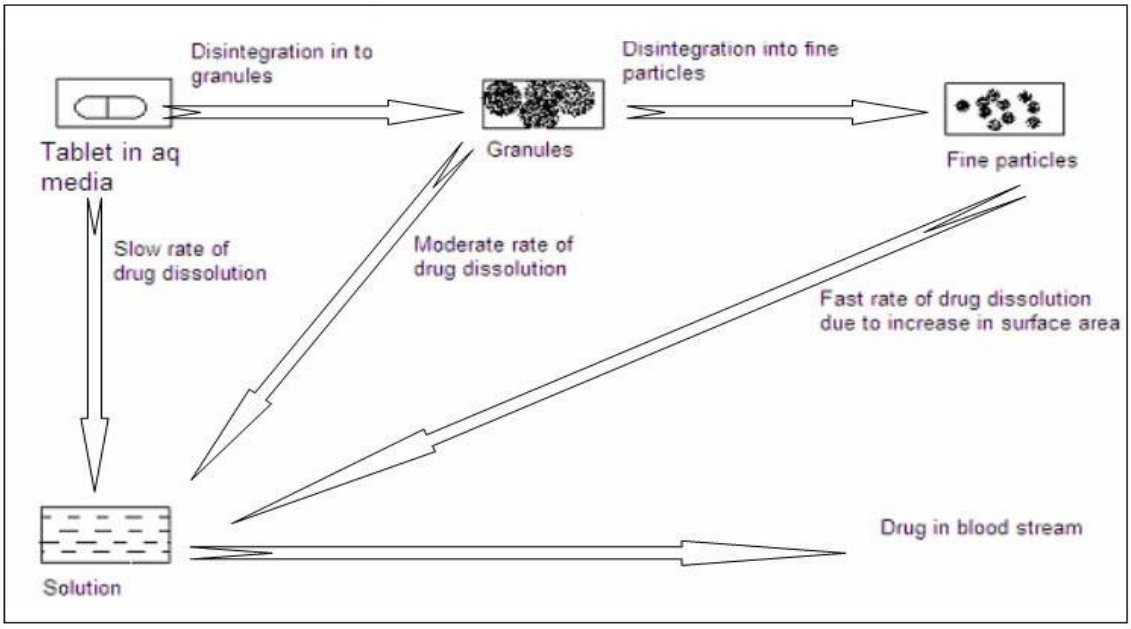
General properties of tablet dosage form:

- A tablet should have elegant product identity while free of defects like chips, cracks, discolouration and contamination.
- Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
- Should have the chemical and physical stability to maintain its physical attributes over time.
- The tablet must be able to release the medicinal agents in a predictable and reproducible manner.

- Must have a chemical stability over time so as not to follow alteration of the medicinal agents.

Use of disintegrants is the basic approach in the development of tablets. Disintegrants play a major role in the disintegration and dissolution of tablet. It is critically essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates.

MECHANISM OF DISINTEGRATION (Arijit Gandhi 2012):

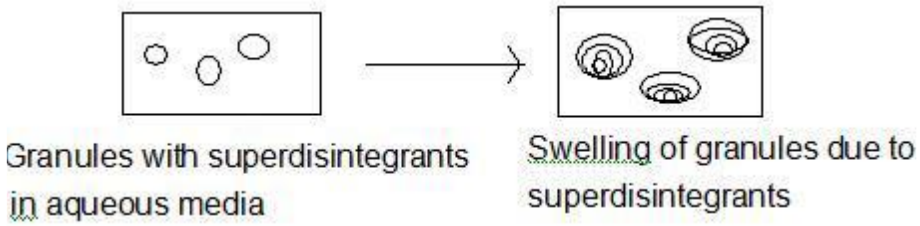


There are four major mechanisms for tablets disintegration as follows:

- Swelling
- Porosity and capillary action (Wicking)
- Disintegrating particle / particle repulsive forces
- Deformation

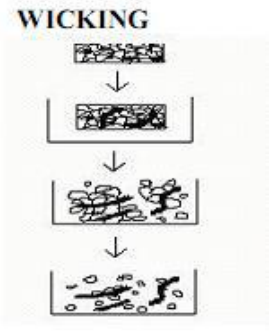
1.Swelling:

The most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity.



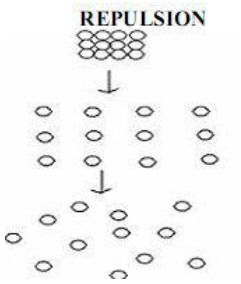
2. Porosity and capillary action:

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.



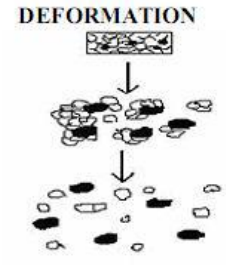
3. Due to disintegrating particle/particle repulsive forces:

Another mechanism of disintegrant attempts to explain the swelling of tablet made with non-swellable disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that no swelling particle also causes disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.



4. Due to deformation:

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet.



TYPES OF TABLETS:

- Uncoated tablets
- Coated tablets
- Effervescent tablets
- Soluble tablets
- Dispersible tablets
- Orodispersible tablets
- Gastro-resistant tablets
- Modified-release tablets

ORODISPERSIBLE TABLETS:

One important drawback of oral solid dosage forms like tablet and capsule is disphagia or difficulty in swallowing, leading to patient incompliance particularly in case of pediatric, geriatric, bed ridden, nauseous patients, unconsciousness, motion sickness, unavailability of water and mentally disabled persons. Drinking water plays an important role in swallowing. Approximately one-third of the population (mainly pediatric and geriatric) has swallowing difficulties resulting in poor compliance with oral dosage form which results in a high incidence of non-compliance and ineffective therapy. To overcome these difficulties pharmaceutical technologists have devoted considerable efforts for developing a novel type of dosage form for oral administration known as orally disintegrating tablets(ODTs) **(Shivam Singh *et al.*, 2017).**

Orodispersible tablets are also called as orally disintegrating tablets, mouth-dissolving tablets, rapid dissolving tablets, fast-disintegrating tablets, fast-dissolving tablets. Recently, European Pharmacopoeia has used the term orodispersible tablets. This may be defined as “uncoated tablets intended to be placed in the mouth where they disperse readily within 3 minutes before swallowing”. The United States Pharmacopoeia has also approved these dosage forms as orodispersible tablets **(Pooja Arora *et al., 2013*).**

SELECTION OF ODT DRUG CANDIDATES: (Adchitre Vaishali *et al.,* 2016)

- No bier taste.
- Dose lower than 20mg.
- Small to moderate molecular weight.
- Good stability in water and saliva.
- Partially non ionized at the oral cavities Ph.
- Ability to diffuse and partition into the epithelium of the upper GIT (log p>1 or preferably>2).
- Short half-life and frequent dosing.

ADVANTAGES OF ODTs: (Ujjwal Nautiyal *et al.,* 2014)

- Ease of administration to patient who cannot swallow such as geriatric, pediatric, mentally disabled, stroke victims and bed-ridden patients, who have difficulty in swallowing the tablet.
- The FDTs do not need water for swallowing unlike conventional dosage forms. This is very convenient for patients who are travelling or do not have immediate access to water, and thus, provide improved patient compliance.
- Being unit solid dosage forms, provide luxury of accurate dosing,

easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.

- Bioavailability of drugs is enhanced due to absorption from mouth, pharynx, and oesophagus.
- Pregastric absorption can result in improved bioavailability and because of reduced dosage, improved clinical performance through a reduction of unwanted effects.
- Rapid onset of therapeutic action as tablet is disintegrated rapidly along with quick dissolution and absorption in oral cavity.
- Good mouth feels, especially for paediatric patients as taste-masking technique is used to avoid the bitter taste of drugs.
- Minimum risk of suffocation in airways due to physical obstruction, when ODTs are swallowed, thus they provide improved safety and compliance with their administrations.
- Rapid drug therapy intervention is possible.
- Conventional processing and packaging equipment allow the manufacturing of tablets at low cost.
- No specific packaging is required. It can be packaged in push through blisters.
- Provide new business opportunities in the form of product differentiation, patent-life extension, uniqueness, line extension, and lifecycle management, and exclusivity of product promotion.

DISADVANTAGES OF ODTs: (Ujjwal Nautiyal *et al.,* 2014)

- Drugs with relatively large doses are difficult to formulate into FDTs.
- Patients who concurrently take anti-cholinergic medications may not be the best candidates for FDTs.
- Tablets usually have insufficient mechanical strength. Hence, it requires careful packaging and handling.
- Tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
- They are more susceptible to degradation by humidity and temperature.

- Fast dissolving tablet is hygroscopic in nature so must be keep in dry place.
- Some time it possesses mouth feeling.
- MDT requires special packaging for properly stabilization & safety of stable product.
- Drugs difficult to formulate into FDT with relatively larger doses.
- Drugs with short half-life and frequent dosing and those whom require controlled or sustained release are unsuitable candidates of FDTs.
- Eating and drinking may become restricted.
- Light sensitive drugs, ODT's may not be suitable as no option for film coating.

CHALLENGES IN FORMULAION OF ODTs: (Anupam Roy *et al.,* 2016)

Mechanical strength and disintegration time

ODTs are formulated to obtain disintegration time usually less than a minute. While doing so, maintaining a good mechanical strength is a prime challenge. Increasing the mechanical strength will delay the disintegration time. So, a good compromise between these two parameters is always essential.

Tastes masking

Many drugs are bitter in taste. A tablet of bitter drug dissolving/disintegration in the mouth will seriously affect patient compliance and acceptance for the dosage form. Hence, effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity.

Aqueous solubility

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented using various matrix-forming excipients such as mannitol that can induce crystallinity and hence, impart rigidity to the amorphous composite.

Size of tablets

The degree of ease when taking tablets depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Amount of drug

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. According to USP generally, the ODT tablet weight should not exceed 500 mg. For lyophilized dosage form, the drug dose should be lower than 400 mg for insoluble drug and <60 mg for soluble drug. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

Hygroscopicity

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

Mouth feel

Larger particles can result in a gritty feeling the oral cavity. Thus, small particles are preferred. Moreover, addition of flavors and cooling agents like menthol improve the mouth feel.

Good packaging design

For the protection of ODTs from moisture and other environmental hazards, the package design should be considered early in the development stages.

CRITERIA FOR EXCIPIENTS USED IN ODTs: (Shivam Singh *et al.,* 2017)

- Their individual properties should not affect the FDTs.
- It must be able to disintegrate quickly.
- It should not have any interaction with drug and other excipients.
- When selecting binder (a single or combination of binders) care
- must be taken in the final integrity and stability of the product.
- The melting point of the excipients used should be in the range of

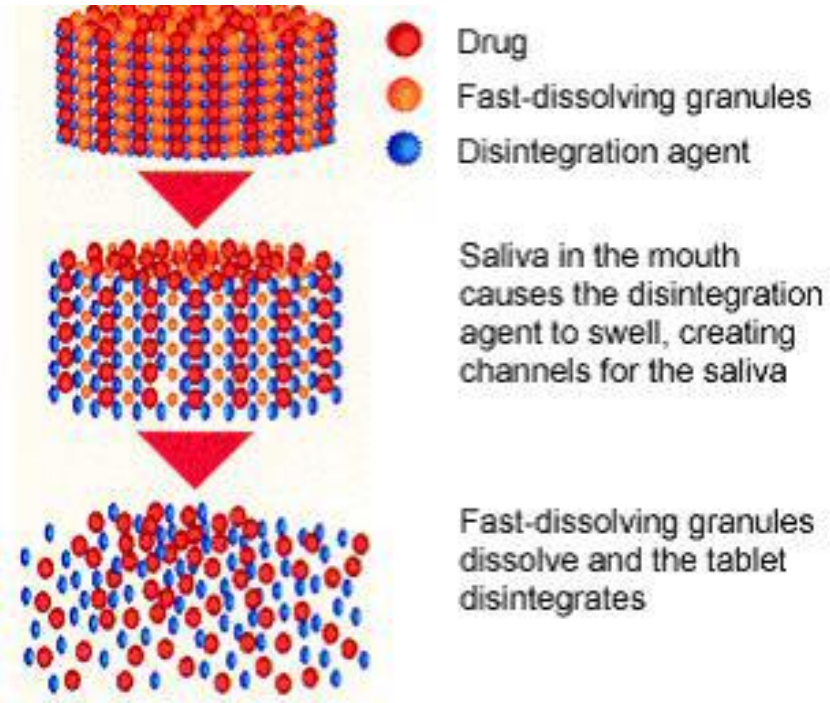
- 30-35 °C.
- It should not interfere in the efficacy and organoleptic properties
- of the product.
- The binder may be in liquid, semi-solid, solid or polymeric in nature.

EXCIPIENTS USED IN FORMULATION OF ODTS:

Excipients used in FDTs contain at least one super disintegrant, a diluent, a lubricant and optionally a swelling agent, a permeabilizing agent, sweeteners and flavouring agents.

SUPERDISINTEGRANTS:

Super disintegrants which are effective at low concentration and have greater disintegrating efficiency, and they are more effectiveintragranular. These superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes the tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.



TYPES OF SUPERDINEGRANTS: (Mohit Mangal *et al.*, 2012)

The Superdisintegrants can be classified into two categories on the basis of their availability:

- Natural Superdisintegrants
- Synthetic Superdisintegrants.

NATURAL SUPERDISINTEGRANTS:

These superdisinegrating agents are natural in origin and are preferred over synthetic substances because they are comparatively cheaper, abundantly available, non-irritating and nontoxic in nature. The natural materials like gums and mucilages have been extensively used in the field of drug delivery for their easy availability, cost effectiveness, Eco friendliness, emollient and non-irritant nature, non-toxicity, capable of multitude of chemical modifications, potentially degradable and compatible due to natural origin. There are several gums and mucilages are available which have super-disintegrating acvtivity.

- **Plantago Ovata Seed Mucilage (Isapgula)**

Isapghula consists of dried seeds of the plant plantagoovata and it contains mucilage which is present in theepidermis of the seeds. The seeds of *Plantagoovata*were soaked in distilled water for 48 hrs and then boiled for few minutes for complete release of mucilage into water. The material was squeezed through muslin cloth for filtering and separating out the marc. Then, an equal volume of acetone was added to the filtrate so as to precipitate the mucilage. The separated mucilage was dried in oven at temperature less than 60°C .The mucilage of *plantagoovata*is a recent innovation for its superdisintegration property when compared with Crospovidone. It shows faster disintegration time than the superdisintegrant,Crosspovidone.

- **Lepidiumsativum Mucilage**

Lepidiumsativum(family: Cruciferae) is known as asaliyo and is widely used as herbal medicine in India. It is widely available in market and has very low cost. Parts used are leaves, root, oil, seeds etc. Seeds contain higheramount of mucilage, dimeric imidazole alkaloids lepidine B, C, D, E and

F and two new monomeric imidazole alkaloids semilepidinosideA and B. Mucilage of Lepidiumsativumhas various characteristic like binding,disintegrating, gelling.

- **Gum Karaya**

Gum Karaya is a negative colloid and a complex polysaccharide of high molecular weight. On hydrolysis it yields galactose, rhamnose and galacturonic acid. Gum Karaya occurs as a partially acetylated derivative. It is a dried exudation of sterculiaUrenstree (Family-Sterculiaceae). Its synonyms are Karaya, sterculia, Indiantragacanth, Bassoratragacanth, kadaya, Kadira,katila. Gum Karaya is compatible with other plant hydrocolloids as well as proteins and carbohydrates.

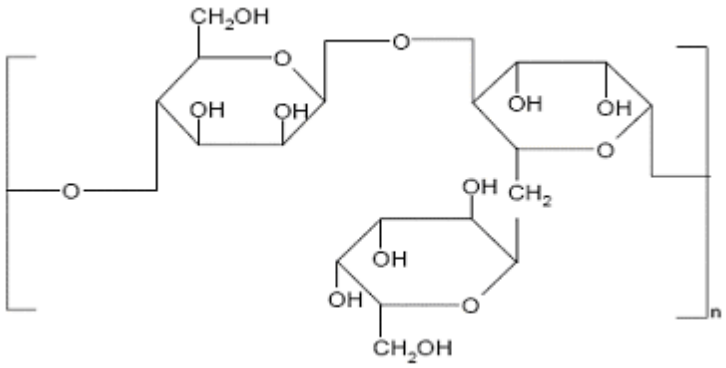
- **Fenugreek Seed Mucilage**

Trigonella Foenum-graceum, commonly known as Fenugreek, is an herbaceous plant of the leguminous family. It has found wide applications as a food, a food additive, and as a traditional medicine. The leaves and both the ripe and unripe seeds of *Trigonella Foenum-graceumare* used as vegetables. Fenugreek has been used in treating colic flatulence, dysentery, diarrhoea, dyspepsia with loss of appetite, chronic cough, dropsy, enlargement of liver and spleen, rickets, gout, and diabetes. It is also used as gastro protective, antiurolithiatic, diuretic, antidandruff agent, Anti-inflammatory agent and as antioxidant. The seed is stated to be a tonic. It also is used in post-natal care and to increase lactation in nursing mothers. Fenugreek seeds contain a high percentage of mucilage (a natural gummy substance present in the coatings of many seeds). Although it does not dissolve in water, mucilage forms a viscous tacky mass when exposed to fluids. Like other mucilage-containing substances, fenugreek seeds swell up and become slick when they are exposed to fluids. The resulting soft mass is not absorbed by the body, but instead passes through the intestines and triggers intestinal muscle contractions.

- **Guar gum**

Guar gum is a galactomannan, commonly used in cosmetics, food products and in pharmaceutical formulations.Guar gum is mainly consisting of the high molecular weight (approximately 50,000-8,000,000) polysaccharides composed of galactomannans and is obtained from the endosperm of the seed

of the guar plant, Cyamopsistetragonaloba (L) Taub. (Synonym-Cyamopsispsoraloides). It is used as thickener, stabilizer and emulsifier, and approved in most areas of the world (e.g. EU, USA, Japan, and Australia). Its synonyms are Galactosol; guar flour; jaguar gum; meprogat; meyprodor. It has also been investigated in the preparation of sustained release matrix tablets in the place of cellulose derivatives such as methylcellulose. In pharmaceuticals, guar gum is used in solid-dosage forms as a binder and disintegrant, and in oral and topical products as a suspending, thickening, and stabilizing agent, and also as a controlled-release carrier. Guar gum has also been examined for use in colonic drug delivery.

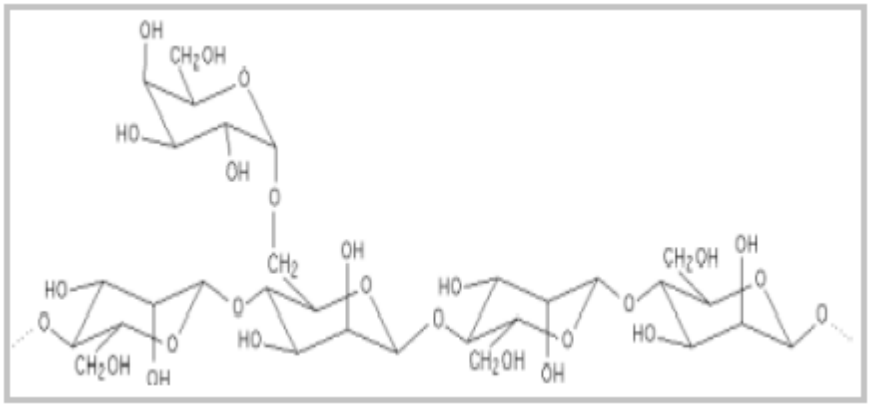


- **Cassia fistula gum**

Seeds of Cassia fistula gum obtained from cassia fistula tree. Gum obtained from the seeds of Cassia fistula comprises β-(1→4) linked d-mannopyranose units with random distribution of _α (1→6) linked d-galactopyranose units as side chain having mannose:galactose ratio of 3.0). Carboxymethylation as well as carbamoylethylation of Cassia gum is reported to improve cold water solubility, improve viscosity and increase microbial resistance as compared to native gum Therefore, an attempt was made to incorporate calcium or sodium salts of carboxymethylated or carbamoylethylated C. fistula gum as superdisintegrant in the formulation development of FDT.

- **Locust Bean gum**

Locust bean gum is extracted from the endosperm of the seeds of the carob tree Ceretoniasiliqua, which grows in Mediterranean countries. It is also called Carob bean gum. Some other familiar polysacharides are starch and cellulose, which are made of long chains of the sugar glucose. In locust bean gum, the ratio of mannose to galactose is higher than in guar gum, giving it slightly different properties, and allowing the two gums to interact synergistically so that together they make a thicker gel than either one alone. It shows as a binder and as a disintegrant property at different concentration. Pharmaceutical application of locust bean gum in various novel drug delivery systems. Locust bean gum has been widely used in food industry as a thickening and gelling agent. Locust bean gum has also been reported to have bioadhesive and solubility enhancement properties. There are various reports that Locust bean gum can be used in pharmaceutical and biotechnological purpose.



- **Hibiscus rosa-sinensis Linn. Mucilage**

Hibiscus rosa-sinensis Linn of the Malvaceae family is also known as the shoe-flower plant, China rose, and Chinese hibiscus. The plant is available in India in large quantities and its mucilage has been found to act as a superdisintegrant. The plant contains cyclopropanoids, methyl sterculate, methyl-2-hydroxysterculate, 2-hydroxysterculate malvate and β-rosasterol. The leaves contain carotene (7.34 mg/100 g of fresh material) moisture, protein, fat, carbohydrate, fibers, calcium, and phosphorus. Mucilage of Hibiscus rosa-sinensiscontains L-rhamnose, D-galactose, D--galactouronic acid, and D-glucuronic acid.

- **Mango Peel Pectin**

Dried mango peel powder is use for extracting pectin. Rather mango peel pectin cannot be used for promising the behaviour of superdisintegrants, but due to its good swelling index and good solubility in biological fluids it can be used to prepare fast dispersible tablets.

SYNTHETIC SUPERDISINTEGRANTS:

A group of superdisintegrants including croscamellose sodium (Ac-Di-Sol) sodium starch glycolate (Primojeland Explotab) and crospovidone (Polyplasdone XL) alleviate most of these problems. Use of the superdisintegrants in fast dispersible tablet is possible as tablet shows optimum physical properties.

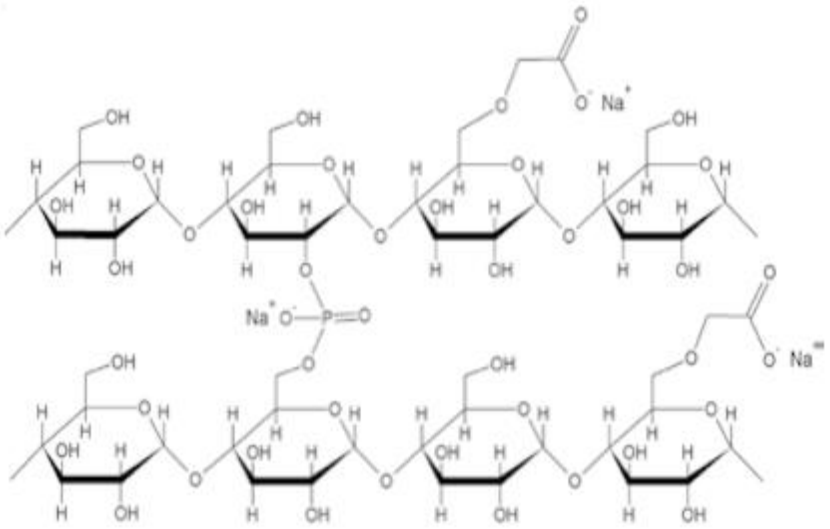
Advantages of Synthetic Superdisintegrants

- Effective in lower concentrations than starch.
- Less effect on compressibility and flow ability.
- More effective intragranularly

- **Sodium Starch Glycolate: (Explotab, Primogel)**

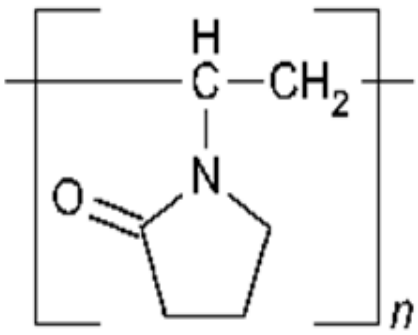
Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is recommended to use in tablets prepared by either direct-compression or wet-granulation processes. The recommended concentration in a formulation is 2-8%, with the optimum concentration about 4% although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.Thedisintegrant efficiency of sodium starch glycolate is unimpaired in the presence of hydrophobic excipients, such as lubricants unlike many other disintegrants. Increasing the tablet compression pressure also appears to have no effect on disintegration time. These are modified starches with dramatic disintegrating properties and are available as explotab and primogel which are low substituted carboxy methyl starches. Explotabconsisting of granules that absorb water rapidly and swell. The mechanism by which this action takes place involves rapid absorption of water leading to an enormous increase in volume of granules result in rapid and uniform disintegration. The natural

predried starches swell in water to the extent of 10-20 percent and the modified starches increase in volume by 200-300 percent in water.



- **Cross-linked polyvinyl pyrrolidone: (crospovidone, PolyplasdoneXL, XL10)**

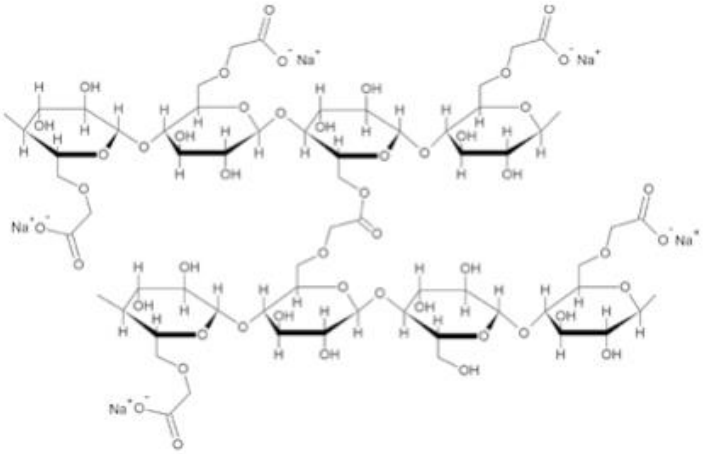
Crospovidone quickly wicks saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth. Unlike other superdisintegrants, which rely principally on swelling for disintegration, Crospovidone superdisintegrants use a combination of swelling and wicking. When examined under a scanning electron microscope, crospovidone particles appear granular and highly porous. This unique, porous particle morphology facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. Due to its high crosslink density, crospovidone swells rapidly in water without gelling. Other superdisintegrants have a lower crosslink density and, as a result, form gels when fully hydrated,particularly at the higher use levels in ODT formulations.Swells very little andreturns to original size after compression but act by capillary action.



Unlike other superdisintegrants, which rely principally on swelling for disintegration, Polyplasdone disintegrants use a combination of mechanisms to provide rapid disintegration. Although Polyplasdone polymers swell by 95% to 120% upon contact with water, swelling is not the only mechanism for tablet disintegration. Swelling or swell volume is mainly a measure of the change in volume of the disintegrant after it is introduced to an aqueous solution and the system has reached equilibrium. However, swell volume does not measure the rate at which a disintegrant absorbs water and swells or the pressure generated by swelling. Polyplasdone polymers, with their porous particle morphology rapidly absorb water (wicking) via capillary action. As the deformed polyplasdone particles come in contact with water that is wicked into the tablet, the polyplasdone particles recover their normal structure and then swell, resulting in rapid volume expansion and high hydrostatic pressures that cause tablet disintegration.

- **Modified Cellulose (croscarmellosesodium, Ac-Di-Sol)**

Croscarmellose sodium is described as a cross-linked polymer of carboxy methyl cellulose (CMC). This polymer is different in synthesis and structure as compare to Sodium starch glycolate. Most importantly, the degree of substitution using Williamson"s ether synthesis of croscarmellose sodium is higher than that of sodium starch glycolate, and the mechanism of crosslinking is also different. The chemistry of SSG is different that of cross carmellose sodium as some of the carboxymethyl groups themselves are used to cross-link the cellulose chains. For example, the cross-linking in Primogel are phosphate ester rather than carboxyl ester links as compare to Cross carmellose sodium. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.



- **Resins**

Resins althoughinsoluble, have great affinity for water and hence, act asdisintegrant. Moreover, because of their smallerparticle size the rate of swelling is high making themsuperdisintegrant. Like conventional disintegrant, theydon"t lump but additionally impart strength to the tablets. The use of ion exchange resins into drug delivery systems have been encouraged because of their physico-chemical stability, inert nature, uniform size, spherical shape assisting coating and equilibrium driven reproducible drug release in ionic environment. Ion exchange resins are insoluble polymers that contain acidic or basic functional groups and have the ability to exchange counter-ions within aqueous solutions surrounding them.Drug, molecules attached to the resins are released by appropriate charged ions in the gastrointestinal tract, followed by diffusion of free drug molecules out of the resins as shown below,

Resin- Drug+ +X+…….....> Resin-....X++Drug+

(1) Resin+Drug-+X-……..>Resin+...X-+Drug

(2) Where, X and Y are ions in the gastrointestinal tract .

BULKING MATERIALS

Bulking materials are important in the development of fast dissolving tablets. They contribute the functions of a diluent, filler and cost reducer. Bulking agents improve the texture of the tablets that consequently enhances the disintegration in the mouth, besides

adding volume and reducing the concentration of the active in the formulation. The bulking agents for this dosage form should be more sugar-based such as

mannitol, polydextrose, lactose derivatives such as directly compressible lactose (DCL) and starch hydrolysate for

higher aqueous solubility and good sensory perception. Mannitol especially has high aqueous solubility and good sensory perception, as it provides a cooling effect due to its negative heat of solution. Bulking agents are added in the range of 10% to about 90% by

weight of the final composition. The descending order of brittleness of excipients is ranked as microcrystalline cellulose>alpha lactose monohydrate>spray-dried lactose>anhydrous beta lactose>anhydrous alpha lactose>> dicalcium phosphate dihydrate. The commonly used sugar-based excipients are especially bulking agents (like dextrose, fructose, lactitol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol) which exhibit high aqueous solubility and sweetness thereby contribute taste masking property and provide pleasant mouth feel. Sugar based excipients can be of types on the basis of moulding and dissolution rate:

Type 1 saccharides: (lactose and mannitol) which exhibit low moldability but high dissolution rate.

Type 2 saccharides: (maltose and maltitol) which exhibit high moldability but low dissolution rate.

EMULSIFYING AGENTS

Emulsifying agents are significant for formulating fast dissolving tablets as they help in quick disintegration and drug release without the need for chewing, swallowing or drinking water. Also, emulsifying agents stabilize the immiscible blends and increase bioavailability. A variety of emulsifying agents for fast dissolving tablet formulations include alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These can be added in the range of 0.05% to about 15% by weight of the final formulation.

LUBRICANTS

Though not essential excipients, these can aid in making the tabletsmore palatable after they disintegrate in the mouth. Lubricants reduce grittiness and help in the drug transit process from the oral to the stomach.

FLAVOURS (TASTE MASKING AGENTS) AND SWEETENERS

Flavours and taste masking agents make the products more palatable and pleasing for patients. The incorporation of these ingredients assists in overcoming bitterness and undesirable tastes of some actives. Natural as well as synthetic flavours can be used to

enhance the organoleptic characteristic of fast dissolving tablets. A wide range of sweeteners including sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose are available. The addition of sweeteners imparts a pleasant taste as well as bulk to the formulation.

TECNOLOGIES USED TO MANUFACTURE ODTs:

COVENTIONAL TECHNOLOGY: (Shivam Singh 2017)

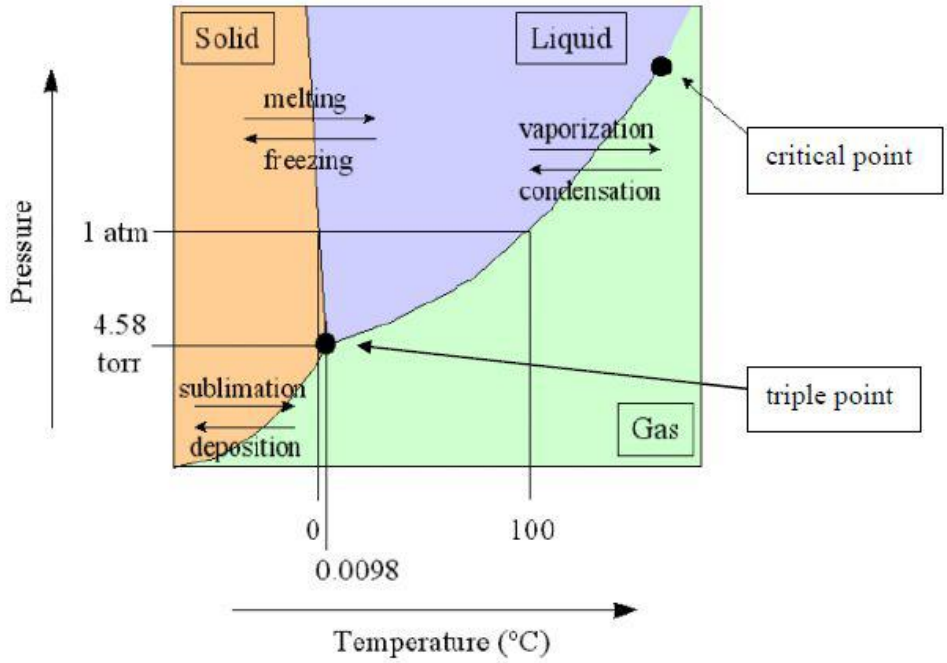
1.Freeze-drying or lyophilization

It is a pharmaceutical process that allows the drying of heat sensitive drugs and biological under low temperature by the application of vacuum to remove water by sublimation. Drugs are dissolved or dispersed in aqueous solution of a carrier, transferred

to preformed blister packs and subjected to nitrogen flush to freeze out, then placed in the refrigerator to complete the process. Characteristics of lyophilization techniques are, they possess high porosity and specific surface area, and gets dissolve rapidly in mouth presenting high drug bioavailability. The major drawback of this system is high cost, time-consuming procedure and fragility, making conventional packing inappropriate for packing this dosage form and stability issues under stress condition.

Advantages

The major advantage of using this technique is that the tablets produced by this technology have very low disintegration time and have great mouthfeel due to fast melting effect.



2.Moulding method

Tablets are designed using hydrophilic ingredients, with the aim to get maximum drug dissolution. Powder mass is wetted with hydroalcoholic solvent and compressed into a dosage form. The solvent system is then allowed to evaporate. Taste of drug particles is developed by spray congealing the molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethene glycol with an active ingredient into lactose based tablet triturate. Characteristics of moulding method are, very porous as solvents are removed by drying leaving porous mass which promotes rapid dissolution.

3.Melt granulation

Melt granulation technique is a process by which the pharmaceutical powders are capably agglomerated by a meltable binder. The benefit of this technique compared to a conventional granulation is that no water or organic solvents is required. Since there is no drying step, the process is less time consuming and requires less energy than wet granulation. It is a technique useful to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin.

4.Mass-extrusion

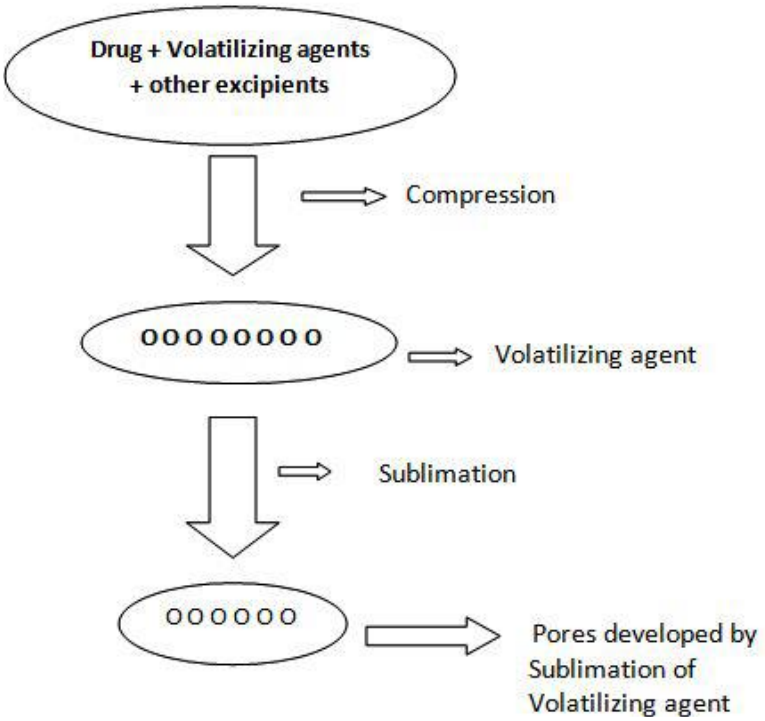
In this the mixed ingredients are softened by water soluble ingredient i.e. polyethene glycol, using methanol as solvent, passing through an extruder to form thin cylinders. Which further get sliced with a heated blade to form small tablets. Characteristics of this method is these products can be used to mask bitter tasting drugs

making small granules thus enhancing oral bioavailability.

5.Sublimation

Rapid disintegration and dissolution is acquired by formulating into porous mass by incorporating inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate and hexamethylene-tetramine. They were mixed with

other ingredients and compressed. The volatile material is evolved by reduced pressure and applying slight temperature leaving the mass in porous form. Characteristics of sublimation method are, they are porous in nature, solvents like cyclohexane and benzene can be used.



6.Direct compression

The disintegrant addition technology (direct compression) is the most preferred technique to manufacture the tablets due to certain advantages:

- High doses can be accommodated and final weight of the tablet can exceed that of other methods.
- The easiest way to manufacture the tablets.
- Conventional equipment and commonly available excipients are used.
- A limited no. of processing steps are involved.
- Cost effectiveness.

Tablet size and hardness strongly affect the disintegrant efficacy. Hard and large tablets have more disintegration time than normally required. Very soft and small tablets have low mechanical strength. So, an optimum kind and concentration of disintegrant should be chosen to achieve quick disintegration

and high dissolution rates. Above the critical concentration level, however, disintegration time remains approximately constant or even increases.

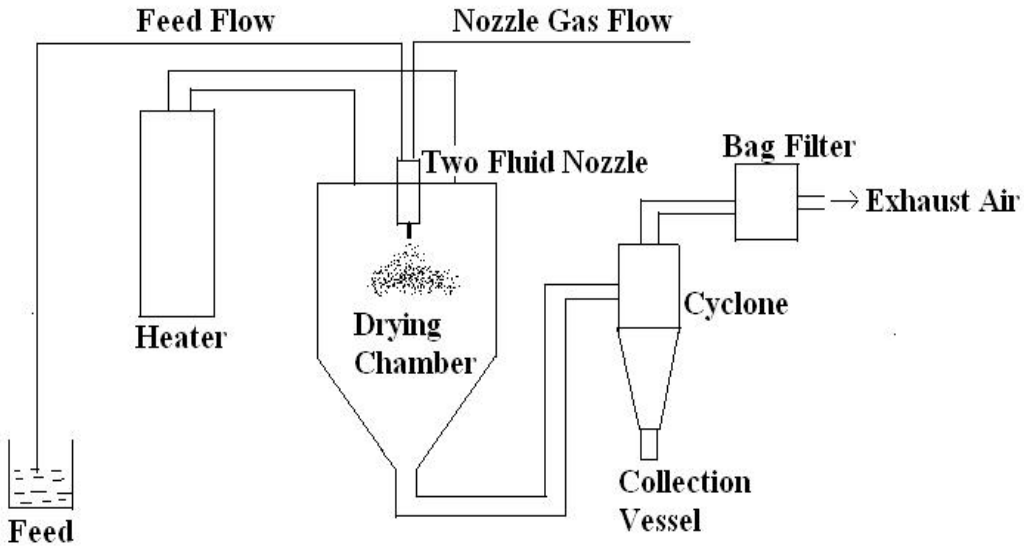
7. Cotton candy process

This process is so named as it utilises a unique spinning mechanism to produce a floss-like crystalline structure, which mimics cotton candy. Cotton candy process involves the formation of Matrix of polysaccharides or saccharides by the simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have improved flow properties and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to FDTs. However, other polysaccharides such as poly maltodextrins and polydextrose can be transformed into fibers at 30-40% lower temperature than sucrose. This modification permits the safe incorporation of thermolabile drugs into the formulation. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouth feel due to fast solubilization of sugars in the presence of saliva.

8. Spray-drying

By this method, ingredients are integrated by hydrolyzed and nonhydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating and an acidic material (e. g. citric acid) and or alkali material (e. g. sodium bicarbonate) to enhance disintegration and dissolution. Characteristics of the spray-drying

method is this method gives rapid dissolution (within 20 seconds) when dosage form gets in contact with the aqueous medium.



9.Phase transition process

This processes for the disintegration of FDTs by phase transition of sugar alcohols using erythritol (melting point 122 °C), xylitol (93-95 °C), trehalose (97 °C), and mannitol (166 °C). Tablets were produced by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. Before the heating process, the tablets do not have sufficient hardness because of low compatibility. The tablet hardness was increased after heating, due to the increase of interparticle bonds or the bonding surface area in tablets induced by phase transition of lower melting point sugar alcohol.

PATENTED TECHNOLOGY: (Kushagra Khanna 2016)

1. **Zydis Technology**

Zydis formulation is a unique technology of preparing fast dissolving tablet. It is freeze dried tablet technology in which drug materials are physically entrapped or dissolved within the matrix of fast dissolving carrier materials.

Water is not required for swallowing because when “zydis unit” is put in mouth then the freeze dried structure disintegrates rapidly. Zydis material is composed of so many substances to achieve a number of objectives. To provide strength during handling polymers such as dextran, alginate and gelatin are incorporated. Saccharides such as sorbitol or mannitol are incorporated to obtain good elegance, hardness and crystallinity. To prevent the shrinkage of “zydis unit” during freeze drying process or long term storage glycine is generally used as collapse protectants. To protect the formulation from the moisture it should be packed in a blister.

2. Durasolv Technology

It is patented technology of CIMA LAB(US patent no.6,024,981) and is based on direct compression technology which uses suitable excipients with improved properties, especially superdisintegrants that accelerate the rate of disintegration and hence dissolution. This technology is based on employment of conventional non-direct compression fillers (such as dextrose, mannitol, sorbitol etc) in the form of fine particles that quickly dissolve without producing a gritty or sandy sensation in the mouth. The water soluble and sometimes effervescent agents can also be use that assist in the disintegration process. The DuraSolv® technology is designed to provide stronger tablets without packaging precautions and can be packed in blisters. In this technology the tablet consists of drug materials, lubricants and fillers.

3. **Orasolv Technology**

CIMA LAB has developed Orasolv technology. Orasolv is an effervescent direct compression tablet that disperses in mouth's saliva with the aid of almost hardly noticeable effervescence and dissolves in less than one

minute, leaving the coated drug powder. The unpleasant flavor of the drug is addressed by coating of the drug powder and effervescence. The major disadvantage of Orasolv is its mechanical strength due to light compression. In Flash dose technology the matrices are prepared by flash heat processing. This technique is patented by fuisz. E.g:Nurofen is the first commercial product by this technology launched by BiovilCorporation.

4. Wow Technology

It is patented by Yamanouchi Pharmaceutical Corporation where wow tends for “without water”. In this process high mouldability saccharide like oligosaccharide, mannitol is mixed with low mouldability saccharide like glucose, lactose and mannitol to obtain rapidly melting strong tablet.

5. Shearform Technology

The core of this technology is preparation of floss. Floss is prepared by subjecting feed stock containing sugar carrier to flash heat process. Sucrose plus either mannitol or dextrose is mixed with surfactant and blended well. This is the primary floss mixture. In flash heat process, the carrier materials show an internal flow condition, which is heat induced and exits via spinning head, and simultaneously under centrifugal force, the floss is flinged.The floss produced by the above way are longer fibers and are further chopped converting them into smaller particles via a high shear mixer granulator. Recrystallization is completed by use of ethanol treatment (1%), spraying out floss, which subsequent evaporation, which increases flow and cohesive properties. This recrystallized matrix is then mixed with drugs and other excipients and subjected to compression. Tablets produced by this process are highly porous,

have a good mouth feel, and have an immediate solubilisation of sugar as it comes in contact with saliva.

6. Flashdose Technology

This technology is much like cotton candy, using a unique spinning mechanism to produce crystalline floss structure. The drug can then be incorporated into this crystalline sugar and compressed into a tablet. Such product has a high surface area for dissolution, dissolving rapidly on tongue and easy dispersion. The Flash dose tablets consist of self–binding shear form matrix termed as “floss”.

7. Ceform Technology

The crux of this process is placing a dry powder containing pure drug and excipients into a rapidly spinning machine. Centrifugal force of the rotating head of this ceform machine, through small heated opening at high speed blends dry drug powder. This drug blend is liquefied to form a sphere, owing to the microburst of heat attained by carefully controlled temperature. This does not affect the stability of the drug. In the preselected oral dosage format the microspheres are blended and/or compressed.

8. Flashtab Technology

sThis technology aims to make the drug have rapid release in GIT, micro encapsulated drug with effervescence, and easily flash dispersal tablet. Usually the polymer used is Eudragit for rapid release. This technology uses conventional approach of wet/dry granulation follow by classical method of compression. Micro-granules of drug, taste masking agents, disintegrating agent, and swelling agents are used to formulate drugs. These tablets have good physical resistance, and highly suggested for hygroscopic materials for

blister packing as materials like polyvinyl chloride/aluminum foils cater better moisture protection in comparison to conventional polyvinyl chloride or polypropylene foils.

CHAPTER – II

LITERATURE REVIEW

LITERATURE REVIEW

Ramanji Reddy *et al.,* (2018), developed and optimized oral disintegtrating tablets of model drug (Lamotrizine) to give quick onset of action by rapidly disintegrating in a few seconds without the need of water with better patient compliance. By performing compatibility studies by IR spectrophotometry, no interaction was confirmed. Oral disintegrating tablets were formulated by direct compression method and evaluated by UV-Visibile spectrophotometer. Prior to compression, the blend of drug and excipients were evaluated for flow properties such as Angle of repose, Bulk density, Tapped density, % Compressibility, and Hausner ratio. All the formulation showed excellentproperties. Oral disintegrating tablets were prepared by direct compression technique using CADMACH 16 station tablet punching machine, equipped with round flat punches of 8 mm diameter. Post compression evaluation of prepared oral disintegrating tablets were carried out with the help of different pharmacopoeial and non-pharmacopoeial (industry specified) tests. The shape and color of all the formulations were found to be circular and white in color. The thickness was found to be uniform in specific formulations. The hardness and friability are also within the permitted limits. Dissolution of tablets was carried out. The crospovidone used formulation gave the more dissolution profile compared to other superdisintegrants.

Jujjuru Naga Suresh *e al.,* (2018), Objective: The main objective of present research investigation is to formulate the Pravastatin Fast Dissolving tablets. Pravastatin. The tablets were prepared employing various concentrations of Crospovidone and Croscarmellose sodium in different combinations as a Superdisintegrants by Direct Compression technique using 3^2 factorial design. The concentration of Crospovidone and Croscarmellose sodium was selected as independent variables, X1 and X2 respectively whereas, wetting time, Disintegration time, t50 ,t90% were selected as dependent variables. the prepared formulations were evaluated for hardness, friability, thickness, Assay, Wetting time, Disintegration time, *In-vitro* drug release. From the Results concluded that all the formulation were found to be within the Pharmacopoeial limits and the *In-vitro*

dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept (a), slope (b) & regression coefficient (r) were calculated. Polynomial equations were developed for Wetting time, Disintegration time, t50%, t90%. Validity of developed polynomial equations were verified by designing 2 check point formulations (C1, C2). According to SUPAC guidelines the formulation (F1) containing combination of 8% Crospovidone and 8% Croscarmellose, is the most similar formulation (similarity factor f2= 89.724, dissimilarity factor f1= 1.307 & No significant difference, t= 0.0465) to marketed product (PRAVACHOL-40). The selected formulation (F5) follows First order, Higuchi's kinetics, mechanism of drug release was found to be Non- Fickian Diffusion Super Case-II Transport (n= 1.875).

Chinmaya Keshari Shahoo *et al.,* (2018), formulated fast dissolving tablets (FDT) of carvedilol by wet granulation method was using super disintegrant crospovidone. Pre compression parameters, post compression parameters, wetting time, in vitro dispersion time, and in vitro dissolution study were evaluated for developed formulation. Compatibility studies of formulations were determined by Fourier Transform Infrared Spectroscopy (FTIR). CP4 formulation showed maximum 91.67 % of drug release at the end of 40 minutes among all 4 formulations. From the FTIR study showed that there were no drug excipient interactions for developed formulation. It was observed that dissolution profile of carvedilol is more in CP4 batch as it contains more amount of crospovidone.

Gabriel Marcelin-Jimenz *et al.,* (2018), formulated the orodispersible tablet (ODT) of mementine and its bioavailability and taste acceptability were evaluated. *In vitro* characterization of ODT comprised dispersion in simulated saliva prior to dissolution assay in a limited volume of biorelevant media. A single oral dose of 20-mg memantine ODT exhibits similar bioavailability to that of an immediate release 20-mg tablet in a healthy population under fasting conditions. 90% confidence interval for Cmax was of 96.78–106.52% and 98.27–104.78% for AUC0–72. An applied palatability survey showed exceptional acceptance of the

formulation. Memantine microspheres prepared by a solid-dispersion technique results in ODT with adequate biopharmaceutical performance.

Shravan Kumar Yamsani *et al.,* (2018), formulated and evaluated oral disintegrating tablets (ODTs) of etodolac to achieve rapid dissolution, absorption and further improving the bioavailability of the drug. The oral disintegrating tablets were prepared by using Croscarmellose sodium, Sodium starch glycolate and Crospovidone in different concentrations by direct compression method. The prepared tablets were evaluated for weight variation, thickness, hardness, friability, drug content, *in vitro* disintegration time, wetting time, water absorption ratio, and *in vitro* dissolution studies. Total nine formulations were prepared (i.e. F1 to F9), out of which tablets with F9 formulation containing 9% crospovidone showed faster disintegration within 15.05 seconds.

Akanksha Sharma *et al.,* (2018), developed febuxostat fast disintegrating tablets with fast release characteristics. Drug and beta cyclodextrin complexes were prepared in the ratio 1:1 and 1:2. Studies show that solubility was better for 1:2 ratio (855.20 µg/ml) as compared to that of pure drug (10.50 µg/ml). Tablets were prepared by using ingredients such as Beta-Cyclodextrin, Crospovidone, Locust Bean Gum, Crosscarmellose, Microcrystalline Cellulose, Mannitol, Magnesium Stereate, Sodium Saccharine.

Pilli Rohini *et al.,*(2017), developed Rosuvastatin Calcium Orodispersible tablets by exploiting the solubilizing effect of β-cyclodextrin (β-CD). Drug–CD complex systems, prepared by different techniques, Precipitation method, Kneading method, and Co-evaporation method, they were characterized by Fourier transform infrared (FT-IR) spectroscopy. The inclusion complex containing RST: β-CD (1:1) was formulated into tablets using superdisintegrants like sodium starch glycolate, Crosspovidone and Crosscarmellose. Tablets containing RST- β-CD inclusion complex were prepared by direct method and evaluated for various post compression parameters like hardness, friability, weight variation, thickness,

drug content and in-vitro dissolution. A significant improvement of the drug dissolution profile was achieved from tablets containing drug–CD systems Kneading method products showed the best dissolution profiles, reaching more than 97.05% drug release at the end of 30 min.

Sheetal Buddhadev et al., (2017), prepared the fast dissolving tablets of Albendazole. In this study, an attempt was made to fasten the drug release from the oral tablets by incorporating the superdisintegrant and camphor/ammonium bicarbonate as subliming agents. The prepared tablets were subjected to pre compression analysis and evaluated for hardness, weight variation, friability, wetting time, water absorption ratio and disintegration time. From the results of in vitro drug release studies, the formulation F9 exhibited fast release profile of about 98.20% in 16 min and disintegration time 65.60 sec when compared with other formulations. For the optimized formulation F9, the initial dissolution rate was 36.5% / 2 min. Fourier transform infrared spectroscopy studies revealed that there was no possibility of interactions between drug and excipients. The present study demonstrated potential for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Rao Baratam *et al.,*(2017), formulated and evaluated fast disintegrating tablets of ondansetron by direct compression method employing natural polymers and modified starches as super disintegrating agents. In the present study an attempt has been made to prepare fast Disintegrating tablets of Linseed, Isapgol, Sodium starch glycolate and Pregelatinized starch used in the level of addition to increase the rate of drug release from dosage form to increase the dissolution rate. Direct Compression method was used to formulate the tablets**.** All the formulations were showed the acceptable flow properties and the pre compression parameters like Bulk density, Tapped density and Carr's compressibility index and Hausner ratio. The post compression parameters like Weight variation, friability, hardness, disintegration, wetting time, water absorption ration, and *In vitro* dissolution profile values were found to be within specified limits. FTIR Studies

shows no interaction between Drug and excipients. From the data obtained, it is observed from the formulation containing Isapgol in Formulation F9, shows Disintegration time in 12 seconds and the Percentage drug release is of 99.10% at the end of 30 min which satisfied all the tablet evaluation parameters for fast disintegrating tablet.

Raghavendra Kumar Gunda *et al.*,(2017), prepared the Fast Dissolving Tablets of Moxifloxacin.HCl employing different concentrations of Crospovidone and Croscarmellose sodium in different combinations as a Superdisintegrants by Direct Compression technique using 3^2 factorial design. The concentration of Crospovidone and Croscarmellose sodium was selected as independent variables, X1 and X2 respectively whereas, wetting time, Disintegration time, t50%, and t90%were selected as dependent variables. Totally nine formulations were designed and are evaluated for hardness, friability, thickness, Assay, Wetting time, Disintegration time, *In-vitro* drug release. From the Results concluded that all the formulation were found to be with in the Pharmacopoeial limits and the In-vitro dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept (a), slope (b) & regression coefficient (r) were calculated. Polynomial equations were developed for Wetting time, Disintegration time, t50%, t90%. Validity of developed polynomial equations were verified by designing 2 check point formulations (C1, C2). According to SUPAC guidelines the formulation (F5) containing combination of 7.5% Crospovidone and 7.5% Croscarmellose, is the most similar formulation (similarity factor f2=68.88, dissimilarity factor f1= 3.35& No significant difference, t= 0.00354) to marketed product (AVELOX-400). The selected formulation (F5) follows First order, Higuchi's kinetics, mechanism of drug release was found to be Non-Fickian Diffusion Super Case-II Transport (n= 1.902).

Ranabir Chanda *et al.,* (2017), developed mouth dissolving tablets of mirtazapine. Mirtazapine, vivasol, explotab, camphor, magnesium stearate, talc, microcrystalline cellulose were used for the preparation of the tablets. The tablets

were prepared by direct compression method and bulk density, tapped density, angle of repose, carr's index, hausners ratio, weight variation, thickness, hardness, friability and *in vitro* drug release were evaluated. Formulation F6 was considered as optimized formulations for mouth dissolving tablet of mirtazapine.

Sandhya V *et al.,* (2017), developed fast disintegrating tablets of Selegiline, using sodium starch glycolate, cross povidone and cross carmellose sodium as super disintegrating agents to enhance the solubility and dissolution rate of drug molecule. Formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density and tapped density. The prepared tablets have shown good post compression parameters and they passed all the quality control evaluation parameters as per IP limits. Among all the formulations F2 formulation showed maximum percentage drug release i.e., 97.26 % in 45 min, hence it is considered as optimized formulation. The F2 formulation contains SSG as super disintegrate in the concentration of 24mg.

Dr Bharathi B *et al., (2016),* developed and evaluated of orodispersible tablets of oseltamivir phosphate. The tablets were prepared by direct compression method using super disintegrants like crospovidone; crosscaramellose sodium; sodium starch glycolate. The FTIR studies results indicated that there was no in-situ interaction between oseltamivir and the selected excipients. Based on the *in vitro* disintegration time, formulations F10, F11 and F12 were found to be promising and displayed *in vitro* dispersion time of 16, 18 and 27 sec respectively.

Kamalinder K singh *et al.,* (2016), developed and evaluated orodispersible sustained release tablet (ODT-SR) of domperidone, which has the convenience of ODT and benefits of controlled release product combined in one. The technology comprised of developing sustained release microspheres (MS) of domperidone, followed by direct compression of MS along with suitable excipients

to yield ODT-SR which rapidly disperses within 30 seconds and yet the dispersed MS maintain their integrity to have a sustained drug release. The particle size of the MS was optimized to be less than 200 µm to avoid the grittiness in the mouth. The DSC thermograms of MS showed the absence of drug-polymer interaction within the microparticles, while SEM confirmed their spherical shape and porous nature. Angle of repose, compressibility and Hausner's ratio of the blend for compression showed good flowability and high percent compressibility. The optimized ODT-SR showed disintegration time of 21 seconds and matrix controlled drug release for 9 h. *Invivo* pharmacokinetic studies in Wistar rats showed that the ODT-SR had a prolonged MRT of 11.16 h as compared 3.86 h of conventional tablet. The developed technology is easily scalable and holds potential for commercial exploitation.

Arifa Begum Shaik *et al.,* (2016), formulated and developed the patient friendly pantoprazole sodium fast dissolving tablets using sublimation method to achieve rapid dissolution. In this study, an attempt was made to fasten the drug release from the oral tablets by incorporating the superdisintegrants and camphor/ammonium bicarbonate as subliming agents. The prepared fast dissolving tablets were subjected to pre compression analysis and evaluated for hardness, weight variation, friability, wetting time, water absorption ratio and disintegration time. From the results of *in vitro* drug release studies, the formulation F9 exhibited fast release profile of about 95.21% in 14 min and disintegration time 90 sec when compared with other formulations. For the optimized formulation F9, the initial dissolution rate was 38.82% / 2 min. Fourier transform infrared spectroscopy studies revealed that there was no possibility of interactions between drug and excipients. The present study demonstrated potential for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Raghavendra Kumar Gunda *et al.,* (2016), formulated the Risperidone Fast Dissolving tablets. The Fast Dissolving tablets of Risperidone were prepared

employing different concentrations of Crospovidone and Croscarmellose sodium in different combinations as a Superdisintegrants by Direct Compression technique using 3^2 factorial design. The concentration of Crospovidone and Croscarmellose sodium was selected as independent variables, X1 and X2respectively whereas, wetting time, Disintegration time, t50% ,t90%were selected as dependent variables. Totally nine formulations were designed, preapred and are evaluated for hardness, friability, thickness, Assay, Wetting time, Disintegration time, *In-vitro* drug release. From the Results concluded that all the formulation were found to be within the Pharmacopoeial limits and the *In-vitro* dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept (a), slope (b) & regression coefficient (r) were calculated. Polynomial equations were developed for Wetting time, Disintegration time, **t50%, t90%**. Validity of developed polynomial equations were verified by designing 2 check point formulations (C1, C2). According to SUPAC guidelines the formulation (F**5**) containing combination of 10% Crospovidone and 10% Croscarmellose, is the most similar formulation (similarity factor f**2**= 93.556, dissimilarity factor f**1**= 0.976& No significant difference, t= 0.022) to marketed product (**RISPERDAL-4**). The selected formulation (F**5**) follows First order, Higuchi's kinetics, mechanism of drug release was found to be Fickian Diffusion (n= 0.383).

Kasar S A *et al.,* (2016), prepared mouth dissolvingtablet of Metoclopramide HCl. Metoclopramide HCl is acting through its prokinetic action increasing gastric emptying. The tablets were prepared by direct compression method using 3^2 factorial designs. Croscarmellose sodium & crospovidone were used as super disintegrants. The tablets were evaluated for weight variation, friability, disintegration time, hardness, wetting time and drug release study. The tablets combination of both croscarmellose sodium and crospovidone showed good results for weight variation, friability, hardness, disintegration time and drug release study.

Jeevitha M *et al.,* (2016), formulated orodispersible tablets of memantine hydrochloride to increase its bioavailability. Orodispersible tablets were prepared by direct compression technique using sublimation approach. The prepared powder mixtures were subjected to both pre and post compression evaluation parameters including; micromeritics properties, tablet hardness, friability, wetting time, disintegration time and in vitro drug release. The results of micromeritics studies revealed that all formulations were of acceptable to good flowability. Tablet hardness and friability indicated good mechanical strength. The F9 formulation which is having high concentration of camphor was given promising results for tablet disintegration, wetting time and gives faster dissolution rate. This increase in the dissolution rate may be due to the presence of crospovidone which is used as a superdisintegrant. This work is helped in understanding the effect of formulation processing variables especially the subliming agent on the drug release profile.

Thirumalesh Naik S B *et al.,* (2016), formulated the orodispersible tablets (ODTs) of Olanzapine (OLZ) by direct compression method for the enhancement of dissolution rate. OLZ ODTs were prepared by direct compression method using co-processed superdisintegrants like sodium starch glycolate (SSG) and Croscarmellose sodium (CCS). It was observed from the evaluation studies that the results were complied with the official limits. In-vitro dissolution studies were carried out by USP dissolution apparatus, paddle method using pH 6.8 phosphate buffer and the formulations F8, F9 showed maximum drug release of 101.16% and 99.45% respectively within 2 min. It was evident from the drug release studies that the formulation F8 and F9 consists of CP-3 showed optimum drug release of 101.80% and 100.33% respectively.

Jitender Mor *et al.,* (2016), formulated fast dissolving tabletes of Losartan potassium by preparing its kneading mixture with crosspovidone. In the first step crosspovidone was examined for suitability as solubility enhancer in kneading method. The characteristics of different kneading mixture samples were compared to the respective physical mixtures and active pharmaceutical ingredient to access

the effect of various processes. Further it was evaluated which technique is better. The solid state of kneading mixture was evaluated with infrared spectroscopy and was correlated with *in-vitro* dissolution behavior.

Prerana Mishra *et al.,* (2016), prepared Fast Dissolving Tablets of nicorandil by direct compression techniques using various concentrations of sodium starch glycolate, croscarmellose sodium, and crospovidone (CP) as superdisintegrants. The optimized batch of fast dissolving tablets of nicorandil were characterized for hardness, friability, *in vitro* disintegration, dissolution, stability studies. In comparison to marketed immediate-release formulation, the formulation (F9) was found to be faster in drug release profile as well as short disintegration time. The formulation F9 were found to be stable in 6 months stability studies in different packing. The results concluded that amongst all the formulations, the formulation containing CP as a superdisintegrant show faster disintegration and dissolution rate.

Geetha K *e al.,* (2016), formulated fast dissolving tablets of Ramipril was design with a view to and provide a quick onset of action. The main objective of the study was to formulate fast dissolving tablets of Ramipril to achieve a better dissolution rate and further improving the bioavailability of the drug. Fast dissolving tablets prepared by direct compression and using superdisintegrants in different concentration and evaluated for the pre-compression parameters. The prepared tablets were evaluated for post compressional evaluation. Among all the 9 formulations the best formulation is with 8 % of crospovidone (CP) showed faster disintegration time within 11sec when compared to the other formulations and it showed 98.6 % drug release at the end of 30 minutes.

Sandhyarani G *et al.,* (2016), prepared orodispersible tablets of domperidone.domperidone drug taste was masked with Amberlite IRP 64 (1:3) effectively. Formulations F1,F2,F3,F4,F5,F6 and F7 are formulated with different concentrations of superdisintegrents by direct compression technique. Formulation

F5 with crosscaramellose and crospovidone with 2mg, 2mg respectively showed better Water absorption ratio 76.73±2.88%, wetting time 26.66±2.08 sec and disintegration time 25±1.0 sec. By considering disintegration time and dissolution time (102.85±0.23 min.) and other evaluation parameters F5 considered as optimized formula for comparision study with marketed Respiridone conventional tablet 38.02% drug released.

Dr Hitesh P Dalvadi *et al.,* (2016), formulated the orodispersible tablets of Amisulpride.The tablets were prepared by using direct compression method, and drug solubility is enhanced by solid dispersion. Formulation were prepared by using different superdisintegrant, combination of different superdisintegrant and effect of hydrophilic lubricant was studied and evaluated pre and post compression parameters. Tablets were evaluated for content uniformity, Disintegration time, wetting time, hardness, friability and *In-vitro* dissolution studies. More than 90% of drug was released from almost all the formulations within 10 min. Formulation C4 containing Sodium starch glycolate (4.5%), Crospovidone (2.5%) and crosscarmellose sodium (3.5%), was having disintegration time 24 seconds, wetting time 18 seconds, hardness 3.4Kg/cm2 and *in vitro* drug release of 99.96% in pH 6.8. Based on this data C4 was found to be the best formulation. Further formulations were subjected to accelerated stability studies. Tablets showed no appreciable changes with respect to disintegration and dissolution profiles. Results of this study indicate among the superdisintegrants tried, combination of superdisintegrant gave the best result.

Kamala Kumari P V *et al.,* (2015), formulated oral disintegrating tablets of amlodipine besylate with a view to achieve a better disintegration and dissolution rate and further improving the bioavailability of the drug and increase the convenient means of administration to those patients suffering from angina pectoris. Oral disintegrating tablets (ODT) of Amlodipine besylate using natural superdisintegrants, synthetic superdisintegrants and coprocessed excipients were prepared by direct compression method. The superdisintegrants used in the study

were crosspovidine and fenugreek seed powder in varying concentrations.2 The prepared tablets were evaluated for pre and post compression parameters such as flow properties, hardness, friability, disintegration time, wetting time, estimation of drug content and *in vitro* drug release studies. The optimized formulation showed the minimum disintegration time of 16 secs and release maximum amount of drug in 30 min. Short term stability studies indicated no significant changes in hardness, friability, *in vitro* disintegration time, drug content and *in vitro* drug release.

Anirudha V Munde *et al.,* (2015), prepared Lansoprazole orodispersible tablets were by direct compression method using varying concentrations of Croscarmellose sodium, Sodium Starch Glycolate, Crospovidone as superdisintegrants. The formulations prepared were evaluated for various parameters like, hardness, weight variation, Friability, *in vitro* dispersion time, water absorption ratio, drug content uniformity and in vitro drug release. The tablets prepared were dispersed in the range of 8.3±0.6-23.7±1.5seconds, the water absorption ratio was 24.9±4.2-186.8±3.2% and the drug was uniformly dispersed in all the formulations in the range of 95.6±0.4-102.5±0.8%. Among the formulation prepared the tablet containing 7.5% of Crospovidone 99.736±0.763% of the drug within 18 min. The overall result indicated that the formulation F6 containing Crospovidone 7.5% is better and fulfilling of the needs of the orodispersible tablets.

Himansu Bhusan Samal *et al.,* (2015), formulated, Evaluated and optimized fast dissolving tablets of Glimepiride. Glimepiride is a Third generation sulphonylureas used for the treatment of type-2 diabetes and belongs to BCS class II drugs (Low Solubility and High Permeability). Glimepiride was the drug of choice because of its low dose. Glimepiride fast dissolving tablets (F1- F18) were prepared using superdisintegrants like Sodium Starch Glycolate, Crosscarmelose sodium, Crosspovidone by employing direct compression technique. Prepared tablets were evaluated for angle of repose, weight variation, Hardness, % friability, wetting time, drug content, disintegration and invitro dissolution studies.The results

of stability studies revealed no change in physical appearance, drug content and in-vitro dissolution profile, thus indicating that formulations was stable. FTIR studies revealed that there was no significant interaction between drug and polymer in the formulations. Among all the formulations (F1-F18), F-15 was found to be optimized as compared to other formulations.

Kameswara Rao S *et al.,* (2015), formulated Enalapril maleate oral disintegrating tablet by using natural and synthetic super disintegrents. ODTs may also be used to deliver drugs to the oral cavity, for local action or, in some cases, absorption across the oral mucosa, thereby avoiding first-pass hepatic metabolism and potentially increasing the rate and extent of uptake, and reducing undesirable metabolites. The objectives of the research work is to formulate oral disintegrating tablets of Enalapril maleate by using different super disintegrates (Natural, Synthetic) in different ratio by direct compression technique and tablets were evaluated for pre compressional and post compressional Parameters such as angle of repose, bulk density, tapped density, compressibility index, drug content and in-vitro drug release study, hardness, friability, wetting time and *in vitro* dispersion time. To study the physical characteristics of the individual drug and optimized formulations by FTIR spectroscopy. To evaluate various characteristics of the resulting tablets. Formulation CCS3, IH2 were subjected to stability Studies as per ICH guidelines at temperatures and humidity of 25±5ºC/60±5%RH; and 40±5ºC/75±5%RH. Tablets didn't reveal any appreciable changes in respect to hardness, disintegration time, drug content and dissolution profile.

Hemalatha K P *et al.,* (2015), developed and evaluated orodispersible tablets of lafutidine. Tablets were prepared by direct compression by using three superdisintegrants of sodium starch glycolate ,crospovidone and Croscarmellose Sodium were used alone as well as in combination. The combination of superdisintegrants gave better disintegration effect. Micro crystalline cellulose was used as diluent, mannitol and aspartame were used to enhance the organoleptic properties of tablets. The dissolution studies were conducted in 900 ml of pH 6.8

phosphate buffer. The optimized formulation F-12 showed good release profile with maximum drug release at all time intervals. The drugs with other excipients were interaction evaluated by FTIR. FTIR spectrum of pure drug was compared with other formulations. All peaks corresponding to the different functional groups of the pure drug were present in the formulations which indicate the absence of interaction between the drug and excipients. The selected formulation F-12 was subjected for stability studies as per ICH guidelines. Formulations subjected for stability studies were checked for drug content, hardness, friability and physical appearance for 90 days with an interval of 15 days. The formulations were found to be stable as no significant change was observed in the various evaluated parameters of the formulations. It was concluded that orodispersible tablets of Lafutidine could be prepared by using blend of all three superdisintegrants. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Gugulothu D *et al.,* (2015), developed sumatriptan succinate orodispersible tablets by freeze drying technology. The tablet excipients were screened and the composition was optimized based on parameters which involved general appearance, tablet size and shape, uniformity of weight, mechanical properties, surface pH, moisture analysis, drug content, wetting time, *in vitro* and *in vivo* disintegration time. Furthermore, Fourier transform infrared spectroscopy, differential scanning calorimetry, scanning electron micrograph of cross- section of the tablet and *in vitro* dissolution studies were performed. Studies revealed that formulation containing gelatin-mannitol (3.75% w/v and 3.5% w/v, respectively) with camphor as a volatile pore forming agent exhibited superior properties with disintegration time of less than 10 s. Furthermore, *in vitro* release studies revealed 90% release of drug from developed dosage form within 10 min, thus suggesting rapid drug dissolution followed by faster onset of action, which formed a strong rationale for development of ODTs of sumatriptan succinate.

Subramanian S *et al.,* (2014), prepared Cetirizine orodispersible tablets to achieve quick onset of action and for maximum bioavailability. Tablets were prepared using cetirizine along with camphor and mannitol in the proportion of 1:1:1, 1:1:3, and 1:1:6. The flow property of granules was found to be good for the formulation CZ2 (1:1:3). The hardness and friability of all the formulations were found to be within the standard limit for orodispersible tablets. Disintegration time was found to be rapid in formulation CZ2 (1:1:3).The *in vitro* dissolution time was found to be 100% in 11 minutes for the formulation CZ2 (1:1:3).

Dr Saleem M A *et al.,* (2014), formulated and evaluated the oral dissolving films of levocetrizine. Levocetirizine is a selective, long acting peripheral H1receptor antagonist. Allergic rhinitis is a symptomatic disorder of the nose induced by inflammation mediated by immunoglobulin E (IgE) in the membrane lining the nose after allergen exposure. Thus, formulating Levocetirizine into a fast dissolving dosage form would provide fast relief. Levocetirizine is bitter in taste so ß-cyclodextrin was used to mask the taste. Inclusion complexes of drug ß-cyclodextrin were prepared by kneading method in 1:1 molar ratios. The prepared inclusion complexes were characterized by FTIR spectroscopy suggesting no interaction. The oral fast dissolving films were prepared by using different polymers like HPMC, PVA, PVP and carbopol 934P with super disintegrants like sodium starch glycolate and croscarmellose sodium. The prepared films evaluated for folding endurance, swelling index, surface pH, *in vitro* disintegration time, drug content, FTIR Study, Scanning electron microscopy and *in vitro* drug release. The physical appearance and folding endurance properties were found to be good and electron microscopy shows that films are clear, colourless with smooth surface without any scratches. The average folding endurance time found within the range of 121 to 198 times. The drug content found to be 93.33% to 98.68% shows uniform mixing of drug in all prepared fast dissolving films. The *in vitro* disintegration time found to be in the range of 15 to 48sec and the surface pH of

the all formulations was in the range of 6.06 to 6.83. The *in vitro* drug release showed 77.77 to 96.80 % drug release within 10 minutes. The formulations F7 to F12 showed highest drug release which contains croscarmellose as superdisintegrant, among these formulations F7, F8 and F11 showed highest drug release.

Jahufar Sathik *et al.,* (2014), prepared bilayer tablet of Montelukast sodium and Levocetrizine HCL for the treatment of asthma and allergic rhinitis. Bilayer tablet of Montelukast Sodium and Levocetrizine HCL was successfully developed. Immediate release of Montelukast was formulated with crosscaramellose sodium and Levocetrizine layer with starch granules as disintegration. IR spectrum revealed that there is no disturbance in the principle peaks of pure drugs of Montelukast sodium and Levocetrizine HCL. This indicates there was no interaction between the drug and excipient.The formulation showed good flow property and compressibility index. The angle of repose was ranged from 25.0˚±1.40 to 31.4˚±0.97 for Montelukast sodium and 25.2˚±1.40 to 29.5˚± 0.68 for Levocetrizine HCL. The compressibility index was found range from 11.6 to 22.2 for Montelukast sodium and 14.1 to 27.8 Levocetrizine HCL. Hausner's ratio was found to be 1.143 to 1.287 for Montelukast sodium and 14.1 to 27.8 for Levocetrizine HCL. The result of the angle of repose indicates good flow property of the granules and the values of compressibility index further showed support for the flow property. The prepared tablets were evaluated for hardness, friability, weight variation, drug content uniformity. The results were found within the limits. Among the various formulations prepared, Formulation F8 with croscarmellose sodium (20%) shows minimum disintegration time and improved dissolution properties compared to formulation F-1 to F-7. This is because of the dual action of wicking and swelling property of disintegrants. The stability studies were carried out for the optimized formula for three months and it show acceptable results. Hence, Montelukast sodium and Levocetrizine HCL bilayer tablets can be used for alternative dosage form in the effective treatment of patients suffering from allergic rhinitis and bronchial asthma.

Reddy *et al*. (2013) prepared quetiapine fumarate taste masked fast dissolving tablets by sublimation technique. Superdisintegrant selected was crospovidone with camphor, menthol, and urea as sublimating agent. The formulated tablets were tested for various post compression parameters like variation in weight, hardness, friability, content uniformity, disintegration time, wetting time, water absorption ratio, and dissolution testing. The powder blend used for formulation was evaluated for the pre-compression parameters. The pre-compression parameters used for bulk characterization were found within prescribed limits and indicated good powder flow characteristics. The results obtained indicated that the amount of crospovidone and camphor significantly affect rate of drug release and disintegration time. The results concluded that fast dissolving tablets of quetiapine fumarate exhibit enhanced dissolution rate, which lead to better drug bioavailability effectiveness and hence patient compliance.

Shobhit S *et al.,* (2013), formulated Mouth Dissolving Tablets (MDTs) of Aceclofenac by direct compression technique. Sodium starch glycolate and crospovidone were employed as superdisintegrants in various concentrations like 2%, 3% and 4% w/w. All prepared tablets were evaluated for weight variation, hardness, drug content, friability, disintegration time, *in vitro* wetting time and percent drug release. MDTs containing 4% w/w concentration of crospovidone gave best results and is therefore considered as the best formula. It had shown 30 s disintegration time, 25 s wetting time and 79.34% *in vitro* release of drug in 25 min.

Mote *et al*. (2013), formulated dispersible tablets of cefpodoxime proxetil by direct compression technique. The composition of dispersible tablet of cefpodoxime proxetil was crosscarmellose sodium, sodium starch glycolate, crospovidone XL10. From the above study it was concluded that process parameter like hardness, thickness and friability has significantly affect on

performance of the dispersible tablet. As the concentration of superdisintegrant increases the drug release also increased significantly. It was observed that the dispersible tablets of cefpodoxime proxetil with crospovidone showed better drug release and disintegration time in comparison to other formulations consisting of croscarmellose sodium & sodium starch glycolate.

Patni Sonal D *et al.,*(2013), formulated fast dissolving tablets of Salbutamol sulphate by direct compression method for better patient compliance and immediate action in asthma. The tablets were prepared by using synthetic superdisintegrants (Croscarmellose sodium and Sodium starch glycolate) and natural superdisintegrant (mucilage of *Plantago ovata* and *Plantago ovata* husk powder) at different concentrations as 2, 4, 6, 8 and 10 %. The *Plantago ovata* mucilage was extracted from the seeds of *Plantago ovata* (Plantaginaceae).The tablets were characterized for weight variation, hardness, friability, disintegration time, wetting time, water absorption ratio, drug content and *in vitro* dissolution tests. The Drug excipients compatibility study was performed by DSC and IR spectroscopy and no incompatibility was found. The tablets were subjected for accelerated stability study at 40°C /75% RH and were found to be stable. The results clearly shows Natural superdisintegrants requires less disintegration time as compared to synthetic superdisintegrants. Hence present study reveals that the fast dissolving tablets prepared by using mucilage of *Plantago ovata* and husk powder of *Plantago ovata* as superdisintegrants having better appearance and rapid disintegration time.

Patel A K *et al.,* (2012), prepared fast dissolving tablets containing Carbamazepine as a model drug using natural and synthetic superdisintegrants such as isolated mucilage of *Plantago ovata* and croscarmellose sodium and sodium starch glycolate respectively by direct compression method. Prepared formulations were evaluated for precompression parameters such as micromeritic properties like angle of repose, %compressibility and Hausner's ratio. Tablets were also subjected to postcompression analysis for the parameters such as

weight variation, hardness, friability, *in vitro* disintegration time, wetting time, drug content, *in vitro* dissolution study, and stability studies. The prepared tablets were characterized by FTIR for drug-excipient compatibility study. No chemical interaction between drug and excipients was confirmed by FTIR studies. The stability study conducted as per the ICH guidelines and the formulations were found to be stable. The results concluded that amongst all formulations prepared with mucilage of *Plantago ovata* showed better superdisintegrating property than the most widely used synthetic superdisintegrant like croscarmellose sodium and sodium starch glycolate.

Vikas Sharma *et al.,* (2012), formulated fast dissolving tablets of Carvedilol using various natural superdisintegrant like *Plantago ovata*, *Lepidium sativum*, Fenugreek and Guar gum. A Direct compression method was used to prepare fast dissolving tablets containing Carvedilol as a model drug using natural superdisintegrants. Prepared formulations were evaluated for Precompression parameters such as micromeritic properties like angle of repose, %compressibility and Hausner's ratio. Tablets were also subjected to Postcompression analysis for the parameters such as weight variation, hardness, and friability, *in vitro* disintegration time, wetting time, drug content and *in vitro* dissolution study. The results concluded that amongst all formulations, the formulation prepared with mucilage of *Plantago ovata* showed better disintegrating property as well as the release profile than the other used natural superdisintegrant.

Himansu Chopra *et al.,* (2012), developed mouth dissolving tablet of levpceirizine hydrochloride that disintegrates rapidly in mouth by using tasteless complex of Levocetirizine and Tulsion-335. Effect of different parameters such as swelling time, resin activation, drug resin ratio as well as stirring time was optimized by taste and percentage drug loading. Formulated DRC (Drug Resin Complex) was characterized by infrared spectroscopy, thermal analysis and X-ray diffraction pattern. Tablets were formulated by wet granulation with PVP as binder, Sodium Starch Glycolate (SSG) and Crospovidone as super disintegrants. In these batches optimum hardness was achieved but disintegration time was found

to be very high as ≥ 70 second, so further trials were planned by using different superdisintegrants such as Croscarmellose sodium, Sodium Starch Glycolate (SSG) as well as Crospovidone by wet granulation method. Tablets formulated with 7.5% crospovidone showed comparatively low disintegration time (25 sec), wetting time (20 sec) and friability (0.60 %) than the other batches. In present study we optimized the conditions required for maximum drug loading of Levocetirizine with Tulsion-335. Among different superdisintergants, crospovidone was found suitable with drug-resin complex to get the low disintegration time, wetting time and friability of tablets.

Rajshree Panigrahi *et al.,* (2012), formulated the fast dissolving tablets of Lisinopril using natural superdisintegrants in combinations. Various formulations were prepared by direct compression using different combinations of natural superdisintegrant i.e. isolated mucilage of Plantago ovata, isolated mucilage of Aloe vera and extracted mucilage of Hibiscus rosasinesis to achieve optimum release profile, disintegration time and hardness. Microcrystalline cellulose was used as diluent and mannitol as bulking agent. The initial compatibility studies between the drug and excipients were carried out using FTIR spectroscopy. The tablets were evaluated for weight variation, hardness, friability, *in-vitro* disintegration time and drug release characteristics. Hardness indicated good mechanical strength around 2-3 kg/cm2 for all the batches. The results of *in-vitro* disintegration time indicated that the tablets dispersed rapidly in mouth within 40 secs. It was concluded that superdisintegrants addition technique is a useful method for preparing orally disintegrating tablets by direct compression method.

Sharma V *et al.,* (2012), developed mouth dissolving tablet that disintegrated rapidly in mouth by using tasteless complex of Levocetirizine and Tulsion-335. Effect of different parameters such as swelling time, resin activation, drug resin ratio as well as stirring time was optimized by taste and percentage drug loading. Formulated DRC (Drug Resin Complex) was characterized by infrared spectroscopy, thermal analysis and X-ray diffraction

pattern. Tablets were formulated by wet granulation with PVP as binder, Sodium Starch Glycolate (SSG) and Crospovidone as super disintegrants. In those batches optimum hardness was achieved but disintegration time was found to be very high as ≥ 70 second, so further trials were planned by using different superdisintegrants such as Croscarmellose sodium, Sodium Starch Glycolate (SSG) as well as Crospovidone by wet granulation method. Tablets formulated with 7.5% crospovidone showed comparatively low disintegration time (25 sec), wetting time (20 sec) and friability (0.60 %) than the other batches. Among different superdisintegrants, crospovidone was found suitable with drug-resin complex to get the low disintegration time, wetting time and friability of tablets.

Lakshmi P K *et al.,* (2011), prepared the orodispersible tablets of ondansetron hydrochloride with synthetic and natural superdisintegrants. Various formulations were prepared by direct compression using different concentrations of natural superdisintegrant *i.e.* isolated mucilage of *Plantago ovata* and synthetic superdisintegrants namely Kyron T-314, crospovidone, and croscarmellose sodium ranging from 0.4% to 2%. The initial compatibility studies between the drug and excipients were carried out using FTIR spectroscopy. The blend was evaluated for additive properties. The tablets were evaluated for physical parameters and *in vitro* drug release. The disintegration time and *in vitro* drug release of optimized formulation (FK5) was compared with that of marketed formulation. The disintegration time was found to be 32 sec as compared to 49 sec for marketed formulation. The dissimilarity (f1) and similarity factors (f2) were calculated for optimized and marketed formulation and values were found to be 9.63 and 52.46, respectively. The optimized formulation was subjected to stability studies for three months. The formulation was found to be stable, with insignificant change in the hardness, disintegration time, drug content and *in vitro* drug release pattern.

Gopal Satishkumar Gandhi *et al.*,(2011), prepared orodispersible tablet of levocetirizine as antihistaminic agent was prepared by direct compression method using crosspovidone, Crosscarmellose and Indion 414, as superdisintegrants. FT-IR study shows that there is no significant interactions occur between drug and excipient. The tablets prepared were evaluated for various parameters like various density parameters, thickness, hardness, friability, disintegration time, wetting time and In-vitro dissolution time. All the parameters were found to be within limits. The developed formulation of levocetirizine batch F8 (10% Indion 414) showed good palatability and dispersed within 30 seconds as compare to crosscarmellose sodium and crosspovidone. When the results were compared with that of convectional tablets was found to be better with respect to simple manufacturing and allergic rhinitis.

Prameela Rani *et al.*,(2010), prepared fast disintegrating tablets of Metformin hydrochloride in the oral cavity with enhanced dissolution rate. The tablets were prepared with Isphagula husk, natural superdisintegrant and Crosspovidone, synthetic superdisintegrant. The pure drug and formulation blend was examined for angle of repose, bulk density, tapped density, Compressibility index and Haussner's ratio. The prepared tablets were evaluated for hardness, tensile strength, drug content, friability and were found satisfactory. The disintegration time in the oral cavity was also tested and was found to be around 10sec. Based on dissolution rate the disintegrants can be rated as Isphagula husk > Crosspovidone. Hence Ishagula husk was recommended as suitable disintegrant for the preparation of direct compression melt-in-mouth tablets of Metformin hydrochloride. All the dissolution parameters were calculated and compared with market tablet. A 3.78 fold increase in the dissolution rate was observed with F4 sformulation when compared to market tablet(Glucophage). It was concluded that the rapidly disintegrating tablets with proper hardness, rapid disintegration in the oral cavity with enhanced dissolution rate can be made using super disintegrants (natural and synthetic).

Nikku D Yadav *et al.*,(2010), prepared fast dissolving tablets of Aspirin used as an analgesic to relieve minor aches and pains, as an antipyretic to reduce fever, and as an anti-inflammatory medication. In the present study, the effects of a natural superdisintegrants and synthetic superdisintegrants were compared in the formulations of fast dissolving tablets (FDT). FDTs of Aspirin were prepared by direct compression method. These tablets were evaluated for weight variation, hardness, thickness, disintegration time, dispersion time, friability, wetting time, water absorption ration and dissolution. Swelling index was also observed with an objective to compare the swelling property of *Plantag ovata* husk with Ac-di-sol, Crospovidone and sodium Starch glycolate. *Plantago ovata* husk showed the highest swelling index. Hence, it is concluded that natural superdisintegrants (husk of *Plantago ovata*) showed better disintegrating property than the most widely used synthetic superdisintegrants like Crospovidone, Ac-di-sol and Sodium starch glycolate in the formulations of FDTs.

Santanu Chakraborty *et al.,* (2008), studied about the effects of a natural superdisintegrant vis-à-vis isolated mucilage of *Plantago ovata* and synthetic superdisintegrants like sodium starch glycolate (SSG) and croscarmellose sodium (Ac-di-sol) were compared in the formulations of fast dissolving tablets (FDT). FDTs of aceclofenac (model drug) were prepared by direct compression method using microcrystalline cellulose as direct compressible vehicle. Those tablets were evaluated for weight variation, hardness, disintegration time, drug content, friability and dissolution. Swelling index was also investigated with an aim to compare the swelling property of mucilage of *Plantago ovata* with SSG and Ac-di-sol. Among all the super disintegrants, *Plantago ovata* mucilage showed the highest swelling index. Hence, the present study revealed that this natural superdisintegrant (*Plantago ovata* mucilage) showed better disintegrating property than the most widely used synthetic super disintegrants like SSG and Ac-di-sol in the formulations of FDTs.

CHAPTER – III

AIM OF WORK

AIM OF WORK

Difficulty in swallowing (dysphagia) is a common problem of all age groups, especially the geriatric and pediatrics, because of physiological changes associated with those groups. Other categories that experience problems in using conventional oral dosage forms include the mentally ill, uncooperative and patients suffering from nausea, motion sickness (kinetosis), sudden episodes of allergic attack or coughing. Sometimes it may be difficult to swallow conventional products due to non-availability of water. These problems led to the development of a novel type of solid oral dosage form called orodispersible tablet, which disintegrates/dissolves rapidly in saliva without the need of drinking water. The faster the drug into solution, quicker the absorption and on set of action.

The basic approach in the development of the ODTs is the use of superdisintegrants. Many approaches have been developed to manufacture ODTs. These include direct compression, lyophilization and molding. The direct compression method is inexpensive and convenient for producing tablets of sufficient mechanical strength.

Many potent drugs have low dose in such cases diluents provide the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size. Usually the range of diluents may vary from 5- 80%. Diluents also synonymously known as fillers are often added to tablet formulations for secondary reasons like to provide better tablet properties such as, to provide improved cohesion, to allow direct compression manufacturing, to enhance flow and to adjust weight of tablet as per die

capacity.

Antihistamines are the drug of choice for Allergic Rhinitis, chronic idiopathic urticaria and seasonal year round allergies and relieve from itching caused by hives (patches of red, swollen, itchy skin). Levocetirizine hydrochloride is a third generation non-sedative antihistamine developed from the second generation antihistamine cetirizine. It works by blocking histamine receptors. It does not prevent the actual release of histamine from the mast cells, but prevents it binding to its receptors. This in turn prevents the release of other allergy chemicals and increased blood supply to the area and provides relief from the typical symptoms of hay fever.

In the present study, orodispersible tablets of levocetirizine hydrochloride, are designed by using synthetic superdisintegrants (crospovidone and croscarmellose sodium) and natural superdisintegrants (hibiscus leaves mucilage and planago ovata seed mucilage). The designed tablets were evaluated for thickness, hardness, friability, weight variation, *in vitro* dispersion time, wetting time, water absorption ratio, disintegration time, drug content uniformity, *in vitro* dissolution rate (in pH 6.8 phosphate buffer), short term stability and drug excipient interactions (IR spectroscopy).

CHAPTER – IV

PLAN OF WORK

PLAN OF WORK

I. PREPARATION OF STANDARD CALIBRATION CURVE:

A. Determination of λmax for Levocetrizine hydrochloride

B. Calibration of Levocetrizine hydrochloride

II. COMPATIBILITY STUDIES FOR DRUG AND EXCIPIENTS:

A. Fourier transform Infra-Red Spectroscopic (FTIR) studies

B. Differential scanning calorimetry(DSC) studies

III. PREFORMULATION EVALUATION OF POWDER BLEND:

A. Angle of repose (θ)

B. Bulk density

C. Tapped density

D. Carr's index (I) or % compressibility

E. Hausner's ratio

IV. FORMULATION OF LEVOCETRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS:

A. Using different super disintegrants

B. By direct compression

V. EVALUATION OF POST COMPRESSION PARAMETERS OF ORODISPERSIBLE TABLETS:

A. General appearance

B. Tablet thickness and diameter

C. Hardness

D. Weight variation test

E. Friability test

F. Uniformity of Drug content

G. *Invitro* drug release study

H. *Invitro* disintegration time

I. Water absorption ratio

J. Wetting time

VI. EFFECT OF SYNTHETIC SUPERDISINTEGRANTS ON RELEASE PROFILE OF LEVOCETRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS

VII. EFFECT OF NATURAL SUPERDISINTEGRANTS ON RELEASE PROFILE OF LEVOCETRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS

VII. COMPARISION OF DISSOLUTION DATA OF LEVOCETRIZINE HYDROCHLORIDE TABLETS CONTAINING DIFFERENT SUPERDISINTEGRANTS

IX. SELECTION OF BEST FORMULATION

X. EVALUATION OF SELECTED FORMULATION

A. Differential scanning calorimetry(DSC) study for best formulation.

B. Fourier transform Infra-Red Spectroscopic (FTIR) study for best formulation.

XI.DRUG RELEASE KINETIC MODEL FOR THE BEST STUDIES

XII.STABILITY STUDIES

CHAPTER – V

MATERIALS AND EQUIPMENTS

MATERIALS AND EQUIPMENTS

MATERIALS	DISTRIBUTORS
Levocetirizine Hydrochloride	Madras Pharma,Chennai.
Microcrystalline cellulose	Madras Pharma , Chennai.
Sodium starch glycolate	Madras Pharma , Chennai.
Crospovidone	.Madras Pharma , Chennai.
Plantago ovata seed	Local market, Madurai.
Hibiscus leaves mucilage	Self made
Mannitol	Madras Pharma , Chennai.
Magnisum stearate	Madras Pharma,Chennai.
Talc	Madras Pharma,Chennai.
Saccharin sodium	Madras Pharma,Chennai.
Aerosil	Madras Pharma,Chennai.

EQUIPMENT AND SUPPLIERS

EQUIPMENTS	SUPPLIERS
Electronic Weighing Balance	A & D Company,Japan.
Multi punch tablet compression machine	B/D tolling compression machine
UV Visible spectrophotometer	Shimazdu UV-1700,Japan
Digital tablet dissolution apparatus	Lab India Disso Apparatus 2000, India
Friabilty test apparatus	Indian Equipment Corporation, Mumbai
Tablet Hardness Tester	Scientific Engineering Corporation
Digital Vernier Caliper	Linker, Mumbai
Disintegration Test Apparatus	Rolex, India
Fourier Transform Infra Red Spectroscopy	Shimadzu, Japan
Hot Air Oven	Industrial Headans, Chennai

CHAPTER – VI

DRUG PROFILE

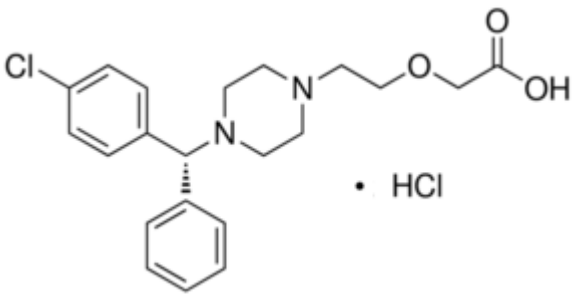
DRUG PROFILE

LEVOCETIRIZINE HYDROCHLORIDE

CHEMICAL NAME

(R)-2-[2-[4-[4-chloro-phenyl) phenyl methyl] piperazin-1-yl] ethoxy] acetic acid hydrochloride.

STRUCTURE



MOLECULAR FORMULA

$C_{21}H_{26}Cl_2N_2O_3$

MOLECULAR WEIGHT

425.35 g/mol

DESCRIPTION

Appearance : A white or almost white powder

Melting point : 130 to 174°C

Boiling point : 346 to 542°C

Density : 1.24gm/cm^3

Refractive index : 1.59

Solubility : Soluble in water

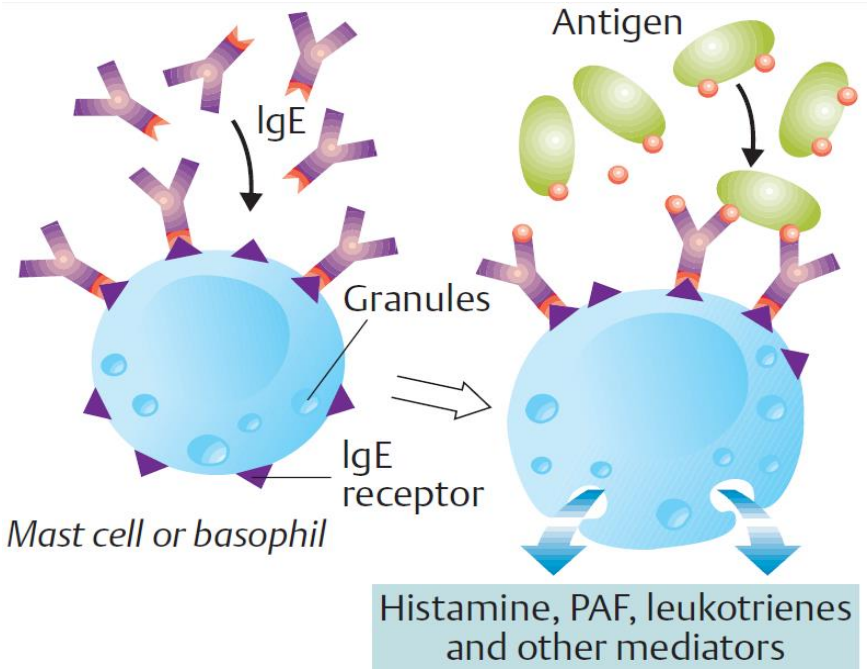
Storage condition : Protect from moisture

MECHANISM OF ACTION

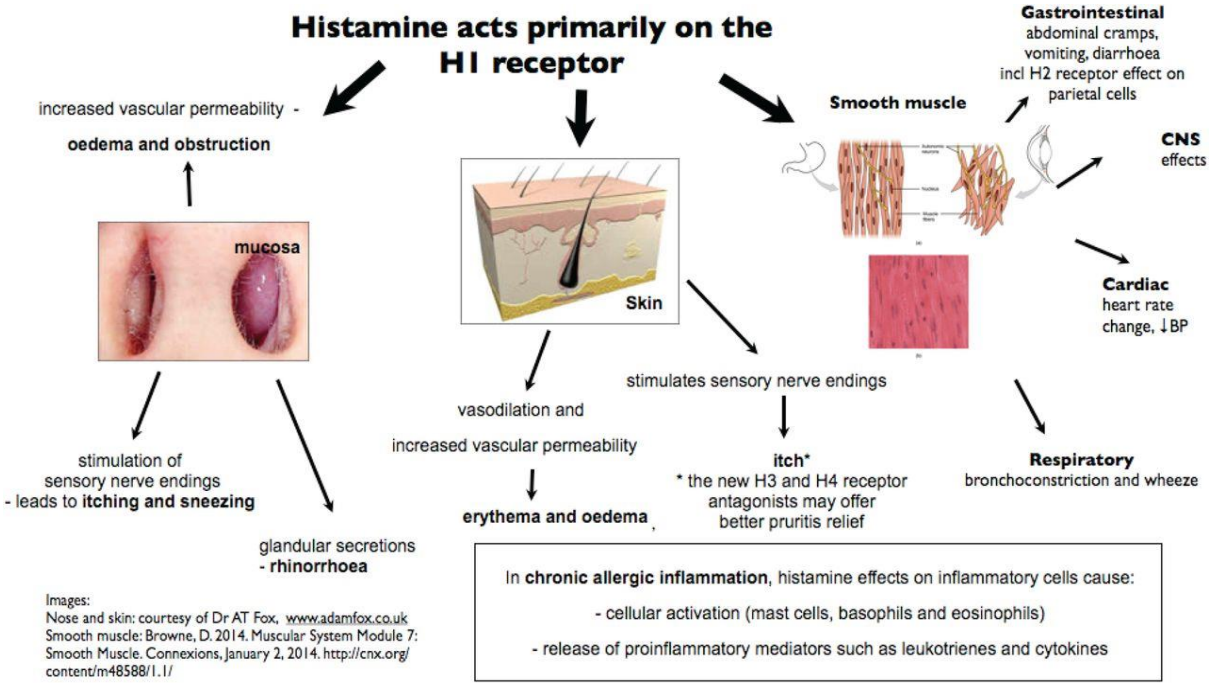
Histamine meaning 'tissue amine' (histos-tissus) is almost ubiquitously present in animal tissues and in certain plants. It was implicated as a mediator of hypersensitivity phenomena and tissue injury reactions. Histamine is present mostly within storage granules of mast cells. Tissues rich in histamine are skin, gastric acid and intestinal mucosa, lungs, liver and placenta. Histamine is also present in blood, most body secretions, venoms and pathological fluids.

SYNTHESIS, STORAGE AND DESTRUCTION

It is synthesized locally from the amino acid histidine and degraded rapidly by oxidation and methylation. In mast cells, histamine (positively charged) is held by an acidic protein and heparin (negatively charged) within intracellular granules. Granules are extruded by exocytosis. Increase in intracellular CAMP (Caused by β adrenergic agonists and methylxanthines) inhibits histamine release.



PHARMACOLOGICAL EFFECT



SECOND GENERATION ANTI-HISTAMINES

Properties

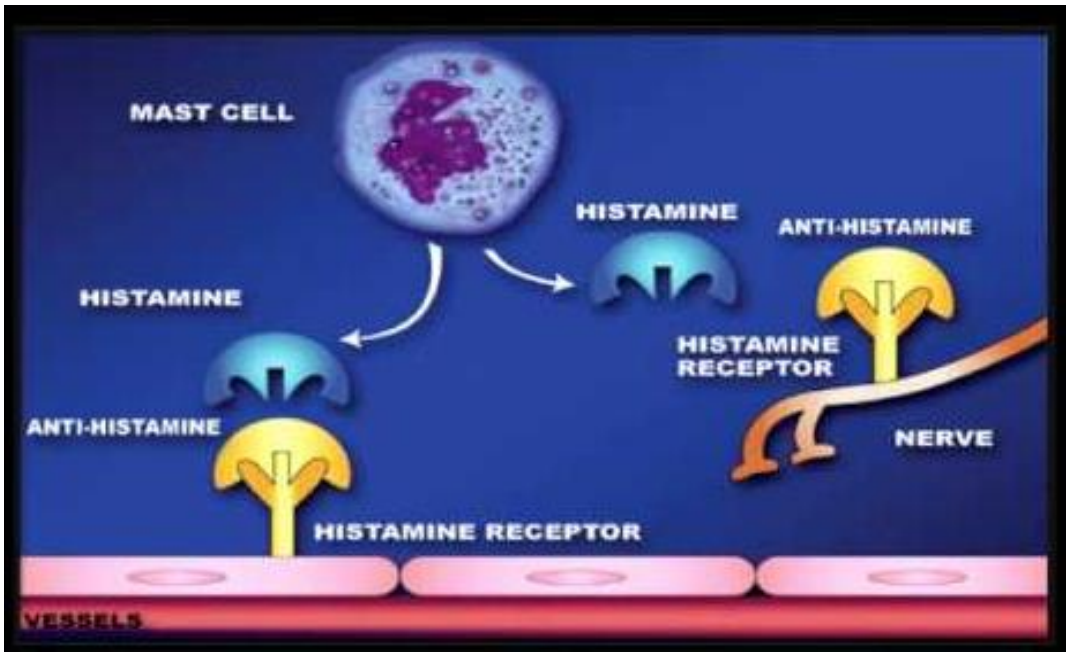
- Absence of CNS depressant property
- Higher H1 selectivity, no anti-cholinergic side effects.
- Additional anti-allergic mechanisms apart from histamine blockade, some also inhibit late phase allergic reaction by acting on leukotrienes or by antiplatelet activating factor effect.
- Minimally or nonsedating because oftheir limited penetration of the blood-brain barrier.

CLASSIFICATION

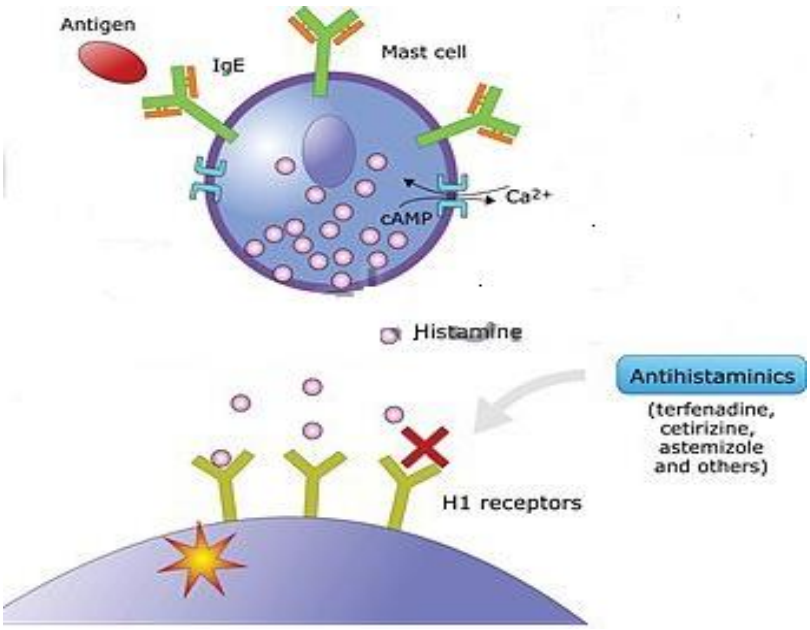
- Fexofenadine
- Loratidine
- Desloratidine
- Cetirizine
- Levocetrizine
- Azelastine

- Mizolastine
- Ebastine
- Rupatadine

Levocetirizine hydrochloride is a second generation antihistamine, developed from the cetirizine. Levocetirizine works by blocking histamine receptors. It does not prevent the actual release of histamine from mast cells, but prevents it binding to its receptors. This in turn prevents the release of other allergy chemicals and increased blood supply to the area, and provides relief from the typical symptoms of hay fever.



Second generation anti-histamines are specific for H_1 receptor selectivity.



PHARMACODYNAMICS

Levocetirizineis the active R-enantiomer of the racemate cetirizine. It is highly selective for the human histamine H_1-receptor, at which it has twice the binding affinity of cetirizine. Levocetirizinecoming under the second generation anti-histamines. It works by blocking the release of a chemical called histaminethat our body makes during an allergic reaction. Levocetirizine was the most potent and consistently effective drug for inhibiting the histamine-induced wheal-and-flare surface areas.This helps relieve symptoms of allergies, such as sneezing, runny nose, and red, watery, itchy eyes. This drug also helps relieve itching caused by hives.

ADVERSE DRUG REACTIONS

Rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.Fatigue, somnolence, dry mouth, nasopharyngitis, pyrexia, cough, epistaxis.

PRECAUTIONS

Drowsiness, tiredness, weakness, sore throat, dry mouth, fever, cough, nosebleed, urinary retention, renal impairment, may impair ability to drive or operate machinery.

OTHER DRUG INTERACTIONS

Additive sedation with alcohol and other CNS depressants.

DOSAGE

The recommended dose of levocetirizine hydrochloride is 5 mg [2 teaspoons (10 ml) oral solution] once daily in the evening. Some patients may be adequately controlled by 2.5 mg [1 teaspoon (5 mL) oral solution] once daily in the evening.It can be taken without regard to food consumption.

FOOD (BEFORE/AFTER)

May be taken with or without food.

LIST OF CONTRAINDICATIONS

Levocetirizine is contraindicated in end-stage renal disease patients (CrCl< 10 mL/min)and patients undergoing hemodialysis.Children 6 months to 11 years of age with impaired renal function.

Do not breast-feed (lactation) while take this medicine (levocetirizine tablets).

CHAPTER – VII

EXCIPIENTS PROFILE

EXCIPIENT PROFILE

CROSPOVIDONE

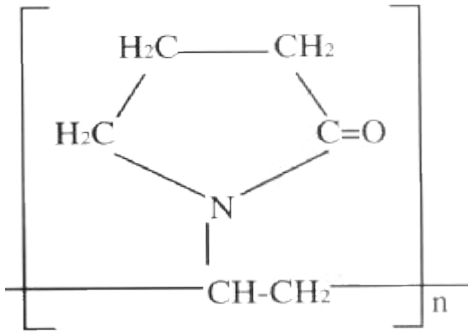
Synonym:

- Cross linked povidone
- Kollido
- 1-vinyl-2-pyrrolidone homopolymer
- Polyplasdone
- Polyvinylpolypyrrolidone

Chemical name :

- 1-Ethylene-2-pyrrolidinone homopolymer

Functional formula :



Empirical formula:

- $(C_6H_9NO)_n$

Molecular weight:

- >1000 000

Functional category:

- Tablet disintegrant.

Application in pharmaceutical formulation or technology:

- Tablet disintergrant and dissolution agent.
- Solubility enhancer for poorly soluble drug

Description:

- Crospovidone is a white-creamy white
- Free flowing
- Practically tasteless
- Hygroscopic powder

Melting Point:

- $150^{O}C$

Stability and Storage condition:

- Crospovidone is hygroscopic
- It should be stored in an airtight container in a cool, dry place.

Incompatibilities:

- Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients.
- When exposed to a high water leval .
- Crospovidone may form molecular adduct with some materials.

Handling Precautions:

- Observe normal precaution appropriate to the circumstances and quantity of material handled.
- Eye protection gloves and a dust mask are recommended

(Hand book of Pharmaceutical Excipients by Raymond C Rowe 5^{th} Edition.)

SODIUM STARCH GLYCOLATE

Nonproprietary Names

- BP: Sodium Starch Glycolate
- PhEur: Sodium Starch Glycolate
- USP-NF: Sodium Starch Glycolate

Synonyms

- Carboxymethyl starch,
- sodium salt;
- carboxymethylamylum natricum;
- Explosol;
- Explotab;
- Glycolys; Primojel;
- starch carboxymethyl ether,
- sodium salt; Tablo; Vivastar P.

Chemical Name

- Sodium carboxymethyl starch

Empirical Formula

- $C_2H_4O_3$ x Na x-Unspecified

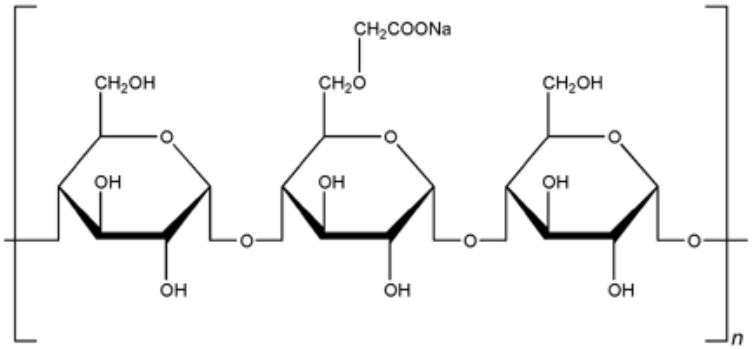
Fragment

- $C_2H_4O_3$ Component Na Unspecified

Molecular weight

- Sodium starch glycolate may be characterized by the degree of substitution and crosslinking. The molecular weight is typically 5 $x10^5$ – 1 x 10^6.

Structural Formula



Functional Category

- Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

- Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations.
- It is commonly used in tablets prepared by either direct-compression or wet-granulation processes.
- The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient..
- Increasing the tablet compression pressure also appears to have no effect on disintegration time.
- Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Description

- Sodium starch glycolate is a white or almost white free-flowing very hygroscopic.

Melting point

- Does not melt, but chars at approximately 200^0C

Solubility

- Practically insoluble in methylene chloride. It gives a translucent suspension in water.powder.

Stability and Storage Conditions

- Tablets prepared with sodium starch glycolate have good storage properties.
- Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.
- The physical properties of sodium starch glycolate remain unchanged for up to 3 years if it is stored at moderate temperatures and humidity.

Incompatibilities

- Sodium starch glycolate is incompatible with ascorbic acid.

Safety

- Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful

Handling Precautions

- Observe normal precautions appropriate to the circumstances and quantity of material handled.
- Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended.
- A dust mask or respirator is recommended for processes that generate a large quantity of dust.

HIBISCUS LEAVES

Genus name : Hibiscus**.**

Synonyms : *Hibiscus* elatus, bladder ketmia, Jamaica sorrel, Confederate rose mallow, red sorrel, swamp rose mallow

Family : Malvaceae

Description : The leaves ate 3.5-12 cm. In length and 2-5.5 cm wide. Leaves are simple ovate or ovate-lanceolate. Leaves are entire at the base and coarsely toothed at the apex.

Description	Hibiscus leaves- β-sitosterol, stigma sterol, taraxeryl acetate and three cyclo propane compounds and their derivatives.
Bulk density	0.142 gm/ml
Tapped density	0.2 gm/ml
Total ash value of crude drug	14 % (w/w)
Acid insoluble ash	5.5 % (w/w)
Water soluble ash	0.5 % (w/w)
Sulphated ash	9 % (w/w)
Loss on drying	86 % (w/w)
Swelling index 1 gm drug make up to 20ml with water	4.5 ml
Foaming index	5 ml conc- 0.5 ml

Properties:

- It is mainly used in the anti-diabetic activity and cosmetics.
- Treating tuberculosis and lung disease. The first benefits is being able to help treat tuberculosis.
- It is used for treating the disease cough.
- It is used for treating the tonsils to swell.
- Treatment for curing colitis.
- Treatment for vomiting blood.
- Can stop bleeding.
- Treatment for hair loss.

Application in pharmaceutical formulation:

- Hibiscus-Rosa Sinesis leaf mucilage exhibit excellent retarding effect on drug release from the floating tablets.
- Hibiscus-Rosa Sinesis leaf mucilage swells well when contact with water in the colon and release the drug in sustained and controlled manner for long time

PLANTAGO OVATA SEED

Genus name : Plantago.

Synonyms : Psyllium seed; Plantain seed; Isabgol; Ishabgul Spogel seed.

Family : Plantaginaceae.

Description : White, pale buff or off white colour.

Composition:

Description	Phylum husk is purely dietary fibrt, composed mostly of hemicelluloses
Mucilloid content	95%
Fibre content	47% soluble fiber
sugars	Arabinose and xylose sugars 24% and 53% respectively.
Moisture-Maxi	10%
Swell volume	40 ml/g
Total Ash- Maxi	4%
Acid insoluble Ash	1% Max

Properties:

- It is a natural product without any chemicals.
- It is non-toxic
- It has high affinity to water. It swells after absorption of water.
- It is emollient, demulcent and laxative.
- It is bland in taste.

Application in pharmaceutical formulation:

- Isphagula husk is widely used in oral pharmaceuticals as a disintegrant in tablets formulation.
- It swells when it come in contact with liquids.

MANNITOL

Synonym:

- Cordycepic acid
- Manna sugar
- D- mannite
- Mannogem
- Pearlitol

Chemical Name:

- D-Mannitol

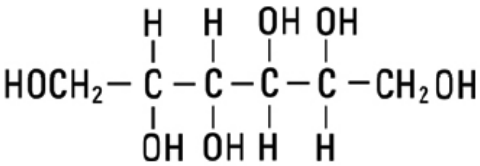
Empirical Formula:

- $C_6H_{14}O_6$

Molecular Weight:

- 182.17

Structural Formula:



Functional Category:

- Diluents
- Sweetening agent
- Tonicity agent

Applications:

- It is used as a diluent in tablet formulations. (10-90% w/v)
- It is used in pharmaceutical formulations and food products.
- It is used in tablet applications include antacid preparation glyceryltrinitrite tablets and vitamin preparations.
- It is used as an excipient in the manufacture of chewable tablet formulation.
- It is also used in sweetness and mouth feel due to its negative heat of solution.
- In lyophilized preparations, mannitol (20-90%w/w) had been included as a carrier to produce a stiff, homogenous cake that improves the appearance of the lyophilized plug in vial.
- It is used in food application as a bulking agent.
- Mannitol administered parentally is used as an osmotic diuretic, it is used in diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure.

Description:

- Mannitol occurs as a white, odourless, crystalline powder or free flowing granule.
- It has a sweet taste, approximately as sweet glucose and half as sweet as sucrose and imparts a cooling sensation in the mouth.
- Mannitol was found to reduce the oral bio availability of cimetidine compared to sucrose.
- Mannitol is reducing sugar, impurities have been implicated in the oxidative degradation of a peptide in a lyophilized formation.

Handling precautions:

- Mannitol is irritant to the eyes; eye protection is recommended.

MICROCRYSTALLINE CELLULOSE

Synonyms :

- Avicel PH
- Crystalline cellulose
- Cellet
- Emcocel
- Hellulosum microcristalinum

Chemical name:

- Cellulose

Empirical formula:

- $(C_6H_{10}O_5)_n$

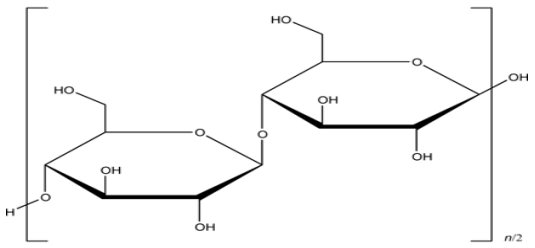
Molecular weight:

- 36000 gm/mol

Functional category:

- Adsorbent
- Suspending agent
- Tablet and capsule diluents
- Tablet disintegrant

Structural formula:



Application in pharmaceutical formulation or technology:

- Microcrystalline cellulose is widely used in pharmaceuticals primarily as binder / diluents in oral tablets and capsule formulation.
- Micerocrystalline cellulose is also used in cosmetics and food products.

Description :

- Microcrystalline cellulose is a white, odorless, tasteless, crystalline powder composed of polrous particles.

Melting Point:

- 260-270^{0}C

Solubility :

- Slightly soluble in 5% w/v NaOH solution ,practically insoluble in water and most organic solvents.

Solubility and storage condition:

- Microcrystalline cellulose is stable though hygroscopic material.
- It should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

- Microcrystalline cellulose is incompatible with strong oxidizing agent.

Handling Precautions:

- Microcrystalline cellulose may be irritant to the eyes, Gloves, eye protection and dust mask are recommended.

(Hand book of pharmaceutical Excipient by Raymond C Rowe.,5th Edition)

SACCHARIN SODIUM

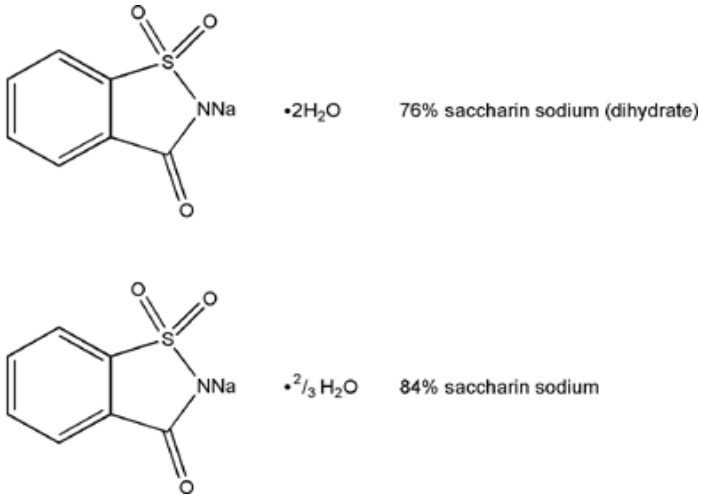
Synonym:

- 1,2-Benzisothiazolin-3-one 1,1-dioxide,sodium salt
- Crystallose
- E954
- Sodium o-benzosulfimide
- Soluble glucose
- Soluble saccharin
- Sucryl sodium

Chemical Name:

- 1,2-Benzisothiazol-3(2H)-one 1,1-dioxide,sodium salt

Chemical Strucure:



Empirical Formula:

- $C_7H_4NnaO_3S$
- $C_7\ H_4\ NNaO_3\ S.\ {}^1/_2H2O$ (84%) 217.24
- $C_7\ H_4\ NNaO_3\ S.\ 2H2O$ (76%) 241.19

Molecular Weight:

- 205.16g/mol

Functional Category:

- Sweetening agent

Description:

- Saccharin sodium occurs as a white, odorless or faintly aromatic, efflorescent, crystalline powder.
- Saccharin sodium can contain variable amount of water.

Properties:

- Acidity/Alkalinity : pH=6.6 (10% w/v aqueous saccharin sodium)
- Density (Bulk) : 0.8-1.1 g/cm^3 (76% saccharin sodium)

  0.86 g/cm^3 (84% saccharin sodium)
- Density (Particle) : 1.70 g/cm^3 (84% saccharin sodium)
- Density (Tapped) : 0.9-1.2 g/cm^3 (76% saccharin sodium)

  0.96 g/cm^3 (84% saccharin sodium)

Melting Point:

- Decomposes upon heating.
- >572^{0}F (Decomposes)

Solubility:

- >(or) = 100mg/ml at 68^{0}F

Specific Surface Area:

- 0.25m^2/g

Stability and Storage Condition:

- Saccharin sodium is stable under the normal range of conditions employed in formulations. Only when it is exposed to a high temperature (125^0C) at low pH(pH2) for one hour does significant decomposition occur. The 84% grade is the most stable of saccharin sodium since the 76% form will dry fyrther under ambient conditions.
- Saccharin sodium should be stored in a well-closed container in a cool, dry place.

Safety:

- The WHO has se a temporary acceptable daily intake up to 2.5 mg/kg body-weight for saccharin, including its salts. In the UK, The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment(COT) has set an acceptable daily intake for saccharin and its salts (expressed as saccharin sodium) at up to 5mg/kg body-weigt.

  LD_{50} (mouse,oral) : 17.5g/kg

  LD_{50} (rat,IP) : 7.1g/kg

  LD_{50} (rat, oral) : 14.2g/kg

Handling Precautions:

- Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and dust mask are recommended.

  (Handbook of Pharmaceuical Excipients by Raymond C Rowe 5^{th} edition, 1710-1715)

AEROSIL

Synonyms:

- Aerosil
- Cab-O-sil
- Colloidal silica
- Fumed silica
- Fumed silicon dioxide
- Silicone dioxide colloidal

Chemical name:

- Silicon dioxide

Empirical formula:

- SiO_2

Molecular weight:

- 60.08

Functional category:

- Adsorbent
- Anticaking agent
- Glidant and Tablet disintegrant
- Emulsion stabilizer
- Viscosity increasing agent

Application in pharmaceutical formulation or technology:

- It is improves the flow properties of the dry powders.
- It is used as an adsorbent dispersing agent for liquids in powders.
- Eliminate hard settling and minimize the clogging of spray nozzle

Description:

- Colloidal silicone dioxide is a light, loose, bluish-white coloured, tasteless, odorless and amorphous powder**.**

Melting Point:

- 1600^{o}C

Solubility:

- Soluble in hot solution of alkali hydroxide. Practically insoluble in water, organic solvents and acids.

Storage condition:

- It should be stored in a well closed container.

Incompatibilities:

- It is incompatibility with diethylstilbestrol preparations.

Handling Precautions:

- A dust mask should be used, when handling small quantity. For large quantities, a dust respirator is recommended.

(www.chemicallab.com and Hand book of pharmaceutical Excipient by Raymond C Rowe., 5th Edition)

TALC

Synonym:

- Altalc
- Hydrous magnesium calcium silicate
- Hydrous magnesium silicate

Chemical name:

- Talc
- Purified talc
- Talcum

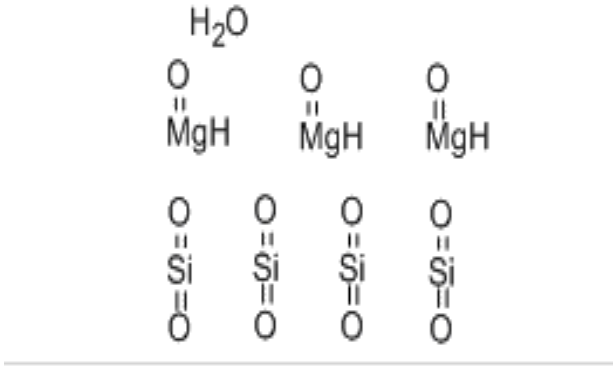
Empirical Formula:

- Talc is purified, hydrated, magnesium silicate.
- Mg6 ((Si2O5)4(OH) 4)
- It may contain small variable amounts of silicate and iron.

Molecular weight:

- 379.27

Structural Formula:



Functional Category :

- Anticaking agent
- Glidant
- Diluent

- Lubricant

Application in pharmaceutical formulation or technology:

- Talc is widely used in solid dosage formulations.
- Lubricant and Glidant. (1.0-10.0)
- Diluents in tablet and capsule. (5.0-30)
- It is widely used as a dissolution retardant in the development of controlled-release products.
- Talc is novel powder coating for extended release pellets and as an adsorbent.
- It is used as a dusting powder. (concentration 90.0-99.0)
- It is used to clarify liquids and is used in cosmetics and food products.
- It is used in baby powder.

Description:

- Talc is very fine, white to grey-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to touch and free from grittiness.

Melting Point:

- 800^{o}C

Solubility:

- Practically insoluble in organic solvent, water and in dilute acids & alkalis.

Stability and Storage condition:

- Talc is a stable material and may be sterilized by heating at 160^{o}C for not less than one hour.
- It may also be sterilized by exposure to ethylene oxide or gamma radiation.
- Talc should be stored in well closed container in a cool, dry place.

Incompatibilities:

- Incompatible with quaternary ammonium compounds.

Handling Precautions:

- Talc is irritant if inhaled and prolonged exposure may cause pneumoconiosis.
- In the UK, the occupational exposure limit for talc is long-term (8 hour TWA). Eye

protection, gloves and respirator are recommended.

(Hand book of Pharmaceutical Excipients by Raymond C Rowe.,5th Edition)

MAGNESIUM STEARATE

Synonym:

- Magnesium octadecanoate
- Octadecanoic acid
- Magnesium salt
- Stearic acid
- Magnesium salt

Chemical Name:

- Octadecanoic acid magnesium salt (557-04-0)

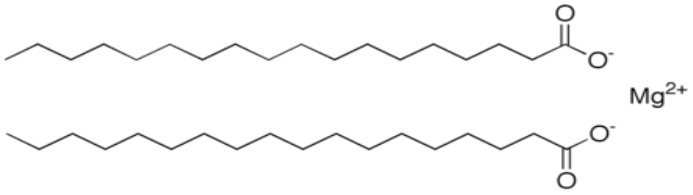
Empirical Formula:

- Magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists of variable proportions of magnesium stearate and magnesium palmitate.
- Magnesium stearate : C36H20MgO4
- Magnesium palmitate : C32H62MgO4

Molecular weight:

- 591.34

Structural Formula:



Functional Category:

- Tablet and capsule lubricant.

Application in pharmaceutical Formulation or Technology:

- It is widely used in cosmetics, foods and pharmaceutical formulations.

- It is used as a lubricant in capsule and tablet manufacture at concentrations 0.25% and 5.0% w/w.

Description :

- Magnesium Stearate is a very fine, light white, precipitated or milled, impalpable
  powder of low density, having a faint odour of stearic acid and a characteristic taste.
- The powder is greasy to touch and readily adheres to the skin

Melting Point:

- 117-150^{O}C

Solubility:

- Slightly soluble in warm benzene and warm ethanol.
- Practically insoluble in ethanol and water.

Stability and Storage condition:

- Magnesium stearate is stable and should be stored in well closed container in a cool, dry place.

Incompatibilities:

- Incompatible with strong acids, alkalis and iron salts.
- Magnesium stearate cannot be used with aspirin, some vitamin and most alkaloidal salts.

Handling Precautions:

- Eye protection and gloves are recommended.
- Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing and choking.

(Hand book of Pharmaceutical Excipients by Raymond C Rowe.,5thEdition).

CHAPTER – VIII

EXPERIMENTAL PROTOCOL

EXPERIMENTAL PROTOCOL

I. CONSTRUCTION OF LEVOCETRIZINE HYDROCHLORIDE CALIBRATION CURVE WITH PHOPHATE BUFFER pH 6.8

Preparation of 0.2M potassium dihydrogen phosphate

27.218g of potassium dihydrogen phosphate was dissolved in distilled water and the volume was made up to 1000 using distilled water.

Preparation of pH 6.8 phosphate buffer solution

Take 50 ml of 0.2M Potassium Dihydrogen phosphate in a 200ml volumetric flask and add 22.4ml of 0.2M Sodium hydroxide solution, then the volume was made upto 200ml using distilled water.

Preparation of 0.2M sodium hydroxide

8g of sodium hydroxide was dissolved in distilled water and made up to 1000ml with distilled water.

a.Determination of λ-max

100mg of Levocetirizine hydrochloride is taken in a 100ml volumetric flask and dissolved by using a small amount of phosphate buffer and made upto 100ml. This stock solution containing 1000µg/ml. This is further diluted into 10µg/ml. The resultant solution is scanned in the range of (200-400nm).

b.Preparation of calibration curve

From the above prepared stock solution, different concentration (2 to 32µg/ml) solutions are prepared. The absorbance of these solutions are measured at λmax (231nm) by UV- spectrophotometer. A standard curve is plotted using concentration on X-axis and the absorbance obtained on Y-axis.

II. COMPATABILITY STUDIES FOR DRUG AND EXCIPIENTS

Compatibility studies are carried out to confirm whether there are no interactions existing between the drug and excipients. It gives information needed for selection of excipients with the drug for the formulation. Infrared spectroscopy and Differential scanning calorimetry studies are the two techniques used to check the compatibility between drug and polymers.

Fourier Transform Infra-Red spectroscopic(FTIR) studies

FT–IR spectra were recorded for levocetirizine hydrochloride pure drug and pure drug with excipients using IR- spectrophotometer. The samples were prepared in KBr dish and scanned over 4000 to 400 cm^{-1}.

III. PRECOMPRESSION EVALUATION OF POWDER BLEND

The goals of the preformulation study are

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine its kinetics release rate profile.
- To establish its compatibility with different excipients.

a. Angle of Repose:

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane

$$Angle\ of\ repose\ (\theta) = tan^{-1}\frac{h}{r}$$

Where,

θ - angle of repose

h - height of pile in cm

r - radius of pile in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property **(Debjit Bhowmik *et al.,* 2009).**

TABLE 1: Limits for angle of repose

ANGLE OF REPOSE	POWDER FLOW
< 25^o	EXCELLENT
25-30^o	GOOD
30-40^o	PASSABLE
>40^o	VERY POOR

b. Bulk Density (Db):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by **(Debjit Bhowmik *et al*., 2009).**

$$Bulk\ density = \frac{mass\ (m)}{bulk\ volume(Vb)}$$

Where,

M - Mass of the Powder

Vb - Bulk volume of the powder

c. Tapped Density:

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume were noted if the difference between these two volumes is less than 2%. If it is more than 2%, then tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by **(Debjit Bhowmik *et al.,* 2009)**

$$Tapped\ density = \frac{mass(m)}{tapped\ volume(Vt)}$$

Where,

M - mass of powder

Vt - tapped volume of the powder.

d. Percentage of compressibility (or) Carr's index:

It indicates powder flow properties. It is expressed in percentage and is given as the Following

$$Compressibility\ index = \frac{tapped\ density - bulk\ density\ X100}{tapped\ density}$$

TABLE 2: Relationship between % compressibility and flowability

% Compressibility	Flow ability
5 – 12	Excellent
12 – 16	Good
18 – 21	Fair passable
23 – 35	Poor
33 – 38	Very poor
< 40	Very very poor

e.Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow. It Is calculated by the following formula **(Debjit Bhowmik *et al.,* 2009)**

$$Hausner's\ ratio = \frac{tapped\ density}{bulk\ density}$$

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

TABLE 3: Relationship between flow characters and Hausner's ratio

Flow characters	Hausner's ratio
Excellent	1.00 – 1.11
Good	1.1 – 1.18

Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 – 1.45
Very poor	1.46 – 1.59
Very very poor	>1.60

IV. FORMULATION OF LEVOCETIRIZINE HYDROPCHLORIDE ORODISPERSIBLE TABLETS

Using different superdisintegrants

- **Synthetic superdisintegrants**
  - -Sodium starch glycolate
  - -Crospovidone
- **Natural superdisintegrants**
  - -Hibiscus leaves mucilage
  - -Plantgo ovate seed mucilage

Isolation of mucilage from hibiscus rosasinensis

The fresh Hibiscus rosasinensis leaves were collected and washed with water. The leaves were crushed and soaked in water for 5-6 hours, boiled for 30 minutes and left to stand for 1 hour to allow complete release of mucilage into water. The mucilage was extracted using a multi layer muslin cloth bag to remove marc from the solution. Acetone (in the quantity of three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated and dried in oven at 35^{o}C, collected, grounded passed through a sieve and stored in a desicator until use.

Isolation of mucilage from plantago ovata seeds

The seeds of plantago ovata were soaked in disilled water for 48hours and then boiled for few minutes for complete release of mucilage into water. The

material was squeezed through the muslin cloth for filtering and separating out the marc. Then an equal volume of acetone was aaded to the filtrate so as to precipitate the mucilage. The separated mucilage was dried in an oven at less than 60^{o}C, powdered, sieved and stored in a desicator until use **(Rajshree Panigrahi *et al.,* 2012).**

By direct compression

All the formulation components other than lubricants and Glidant were accurately weighed, passed through 60-mesh sieve and mixed well for 30 min. Talc and magnesium stearate were passed through 80-mesh sieve, mixed with above blend for 10 min and resultant blend was directly compressed into tablets. The amount of all tablet components other than superdisintegrant and diluents were kept constant. Round flat tablets of 200 mg weight and 8 mm diameter were prepared using 12 station B/D tolling compression machine by direct compression technique.**(kalyankar *et al.,* 2015).**

V. EVALUATION OF POST COMPRESSION PARAMETERS OF LEVOCETIRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS

General appearance

The general appearance of a tablet, its visual identity and over all “elegance” is essential for consumer acceptance. Tablet’s size, shape, colour, surface texture, physical flaws and consistency are noted.

Tablet thickness & diameter:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness and diameter can be measured using a simple procedure. 3 tablets were taken and their thickness and diameter was measured using digital Vernier calipers. **(Amit Modi *et al.,* 2012).**

Tablet hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and

handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Pfizer hardness tester **(Mukesh *et al.,* 2008).**

Uniformity of weight:

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity **(Mukesh *et al.,* 2008).**

TABLE 3: I. P. SPECIFICATION FOR UNIFORMITY OF WEIGHT

AVERAGE WEIGHT OF TABLET	% DEVIATION
80mg or Less	± 10
More than 80mg but less than 250mg	± 7.5
250mg or more	± 5

Friability

It is measure of mechanical strength of tablets. Roche Friabilator was used to determine the friability by following procedure. A preweighed tablet was placed in the Friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the Friabilator for at least 4 minutes. At the end of test tablets they were disused and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as **(Mukesh *et al.,* 2008)**

% friability = loss in weight / initial weight × 100

$$\% \, friability = \frac{w_0 - w_f}{w_0} x100$$

Uniformity of drug content:

Randomly Ten tablets of formulation were weighed and crushed in mortar and powder equivalent to 200mg of levocetirizine hydrochloride was weighed and dissolved in phosphate buffer pH 6.8, the volume was made up to 100ml. From the stock solution 10ml sample was withdrawn and diluted to 100ml with phosphate buffer Ph 6.8. The absorbance was measured at wavelength 231 nm using UV-Visible spectrophotometer. Content uniformity was calculated using formula **(Amit Modi *et al.*, 2012).**

***In vitro* dissolution studies**

Dissolution rate was studied by using USP type –II apparatus (dissolution test apparatus at 50 rpm) using 500 ml phosphate buffer pH 6.8 as dissolution medium. Temperature of the dissolution medium was maintained at 37 ± 0.5^0C, sample was withdrawn at every 5 min interval and diluted suitably and the absorbance of solution was measured by UV spectrophotometer method at 231 nm and concentration of the drug is determined from the standard calibration.

***In vitro* release studies details:**

Apparatus used	:	USPXXIII dissolution test apparatus
Dissolution medium	:	phosphate buffer pH 6.8
Dissolution medium volume	:	500ml
Temperature	:	37 ± 0.5^0C
Speed of paddle	:	50rpm
Sampling intervals	:	5 min
Sample withdraw	:	10ml

Absorbance measured : 231nm

***In vitro* disintegration time**

The test was carried out on 6 tablets using the apparatus specified in IP 2010 distilled water at $37^{O}C \pm 2^{O}C$ was used as a disintegration medium and the time in seconds taken for the entire tablet to disintegrate completely **(Shallesh Sharma *et al.,* 2008).**

Disintegration time

- Uncoated tablets : 5 -30 minutes
- Coated tablets : 1- 2 hours
- Fast dissolving tablets : less than 3 minutes (European pharmacopeia)

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and time required for complete wetting was measured. Three tablets from each formulation were prepared and standard deviation was also determined **(Venkateswara *et al.*, 2014).**

The wetted tablet was then weighed. Water absorption ratio R, was determined using equation-

$$R = 100 \times Wa\text{-}Wb / Wb$$

Where,

Wb = weight of the tablet before water absorption

Wa = weight of the tablets after water absorption

Wetting time

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water or eosin dye and a tablet was put on the paper. The time for complete wetting was measured. Three trials for each batch were

performed and standard deviation was also determined **(venkateswara *et al.,* 2014).**

VI. EFFECT OF SYNTHETIC SUPERDISINTEGRANTS ON RELEASE PROFILE OF LEVOCETIRIZINE HCl ORODISPERSIBLE TABLETS

VII. EFFECT OF NATURAL SUPERDISINTEGRANTS ON RELEASE PROFILE OF LEVOCETIRIZINE HCl ORODISPERSIBLE TABLETS

VIII. COMPARISION OF DISSOLUION DATA OF LEVOCETIRIZINE HCl ORODISPERSIBLE TABLETS CONTAINING DIFFERENT SUPERDISINTEGRANTS

IX. BEST FORMULATION SELECTION

The selection of best formulation is done based on rate of Levocetirizine Hydrochloride release from the *in vitro* dissolution studies.

X. EVALUATION OF SELECTED FORMULATION

a.Fourier transform Infra-red (FTIR) spectroscopic studies for best formulation:

Levocetirizine hydrochloride orodispersible (best formulation) are subjected to infrared spectroscopic studies as per the procedure already discussed in compatibility studies.

b.Differential scanning calorimetry (DSC) for best formulation:

Differential scanning calorimetry is used for screening. The specified samples is hermetically sealed aluminium pans at temperature 20^{O}C/min nitrogen werepurged at 50ml/min and 100ml/min through cooling unit **(Himansu Chopra *et al.,* 2012).**

c.Powder X-Ray Diffraction:

Powder X-ray diffraction is a unique method in determination of crystallinity of a compound. It is used in distinguishing between amorphous and crystalline material. Crystal is composed of periodic arrangement of atoms whereas amorphous atoms do not possess that periodicity. When there is periodic arrangement of atoms, the x-ray will be scattered only in certain direction. This will cause high intensity peaks. In amorphous phase, x-rays will be scattered in many direction leading to large bump distributed in a wide range instead of high intensity narrower peak.

XI. EVALUATION OF INVITRO RELEASE KINETICS

To study the invitro release kinetics of the sublingual tablets, data obtained from invitro dissolution study were plotted in various kinetics models.

1. Zero order release rate kinetics

The zero order order release kinetics can be obtained by plotting cumulative % drug released Vs time (hours).

$$C=K_0 t$$

Where K_0 = Zero order constant in conc/time

t= time in hours

2. First order release rate kinetics

The graph was plotted as log% cumulative drug remaining Vs time in hours.

$$LogC=logC_0 – Kt/2.303$$

C_0=Initial drug concentration

K= First order constant

t = Time in hours

3. Higuchi kinetics

The graph was plotted with % cumulative drug released Vs squre root of time.

$$Q = K t^{1/2}$$

Where K= constant reflecting design variable system

t= time in hours

The drug release rate is inversely proportional to the square root of time

4. Hixson and Crowell erosion equation

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and crowell erosion equation. The graph was plotted by cube root of % drug remaining Vs Time in hours.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} X t$$

Q_t = Amount of drug released at time t

Q_0 = Initial amount of drug

K_{HC} = Rate constant for Hixson crowell equation

5. Korsmeyer – peppas equation

To evaluate the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released Vs log time.

$$M_t / M_\alpha = K t^n$$

Where, M_t / M_α = Fraction of drug release at time t

t = release time

K= Kinetics constant

N=Diffutional exponent indicative of the mechanism of drug release

If slope values is 0.5 or less, the release mechanism is “Fickian diffusion” and if 0.5<n<1 it follows “Non Fickian diffusion” (anomalous transport). The drug release follows zero order drug release and Non-Fickian case II transport if the values is 1. For the values of n higher than 1, the mechanism of drug released is regarded as non-fickian case II transport. The model is used to analyse the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release is involved.

XII. STABILITY STUDIES

The purpose of stability testing is to provide evidence on how quality varies with time. The orodispersible tablets are stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification. The purpose of stability testing is to provide evidence on how the quality of a drug substances or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf lives to be established. In the present studies, stability studies were carried out at 25ºC (room temperature) and $40^{O}C \pm 2^{O}C$/ 75 %RH for a specific time period up to 30 days for selected formulation.

Method

The selected formulations were packed in aluminium boiled paper, they were then stored at $25^{O}C$ (room temperature) and $40^{O}C \pm 2^{O}C$ / 75% RH for 30 days and evaluated for their hardness, drug content and disintegration time and % drug release (Abdul S. Althaf *et al.,* 2011).

CHAPTER – IX

RESULTS AND DISCUSSION

TABLES AND FIGURES

RESULTS AND DISCUSSION

I. PREPARATION OF STANDARDCALIBRATION CURVE FOR LVOCETIRIZINE HYDROCHLORIDE

Determination of λ-max

The absorption maximum (λmax) of the Levocetirizine hydrochloride was estimated by scanning the drug solution (10µg/ml) between 200-400 nm regions on UV spectrophotometer. The obtained spectrum showed that the absorption maximum (λmax) was 231nm for the levocetirizine hydrochloride. **FIG.1**

Calibration of lecocetirizine hydrochloride in phosphate buffer pH 6.8

The Standard Calibration curves of levocetirizine hydrochloride were prepared using phosphate buffer pH 6.8. The absorbance were measured at λmax of 231nm. The correlation coefficient was found to be 0.99978. Cilnidipine obeys the beer's law within the concentration range of (2-16µg/ml). Calibration plot of levocetirizine hydrochloride in phosphate buffer pH 6.8 was shown in **FIG.2 and Table 1.**

II. COMPATABILTY STUDIES FOR DRUG AND EXCIPIENTS

Fourier Transform Infra-Red Spectroscopic (FT-IR) Studies

FT-IR spectrum of the pure drug and mixture of pure drug and excipients used in the formulation were recorded. The spectra of pure levocetirizine hydrochloride showed characteristic peaks at 1743.65 cm^{-1}(-COOH stetching), 2947.23cm^{-1} (-CH_2 stretching), 758.02 cm^{-1} (-C-Cl stretching). All the above peaks were also observed in the spectra of mixture of levocetirizine hydrochloreide and excipients with slight deviations. This indicating that the drug is stable and there is no drug-

excipient interaction **(Bhaskar Umarji et *al.,* 2012) Fig. 3A, 3B, 3C, 3D,3E, 3F, 3G, 3H and 3I .**

III. PREFORMULATION EVALUATION OF POWDER BLEND

The prepared tablets were evaluated on various parameters such as thickness and diameter, hardness, weight variation, friability, uniformity content, wetting time, water absorption ratio, *In-vitro* disintegration time and *In-vitro* dissolution test. The results were summarized in **Table 3**.

Angle of repose

The angle of repose was used to determine the flow properties of powder blend. The angle of repose of the formulations ranged from 27˚29' to 34˚ 32'.The results indicated that the formulations with synthetic superdisintegrants exhibited good flow properties whereas the natural superdisintegrants had a passable flow property. The results of angle of repose for all the formulations were shown in **Table 3** and **FIG. 6**.

Bulk density

The bulk density is used as an index of the ability of the powder to flow. The bulk density of the formulations was in the range of 0.65 – 0.78 g/ml. The values of bulk density showed that the blend was not tightly packed and indicated good flow properties for synthetic super disintegrants and passable for natural super disintegrants diluents. The results of bulk density for all the formulations were shown in **Table 3** and **FIG. 7**.

Tapped density

The tapped density was used to access the free flowing properties of powder blend. The tapped density of the formulations were in the range of 0.74-0.87 g/cm^3.The results indicated that the blends of the formulation had good flow properties for synthetic superdisintegrants and passable for natural superdisintegrants. The results of tapped density for all the formulations were shown in **Table 3** and **FIG. 8**.

Carr's compressibility index

The Carr's compressibility index was used to access the free flowing properties of powder blend. The compressibility index of all the formulations ranged from 8.693 – 12.985%. The value below 16% has a good flow property and good propensity of compression. The results of compressibility for all formulations were shown in **Table 3** and **FIG. 9**.

Hausner's ratio

The Hausner's ratio was an indirect index of ease of powder flow. The Hausner's ratio of all the formulations ranged from 1.1-1.148. This indicates better flow property of blend. The results of Hausner's ratio for all the formulations were shown in **Table 3** and **FIG.10**.

IV. FORMULATION OF LEVOCETIRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS

The orodispersible tablets of Levocetirizine Hydrochloride was prepared by direct compression method using synthetic superdisintegrants (sodium starch glycolate and crospovidone) and natural superdisintegrants (hibiscus leaves mucilage and plantago ovata seed mucilage). The compositions of the different formulation were given in **Table 2A and 2B.** Twelve Formulations (F1 to F12) were prepared as per formula designed. All the tablets were white color and round in shape having 8 mm diameter.

V. POST COPMRESSION EVALUATION

a. General appearance

The tablets were white coloured and round shaped. All tablets were elegant in appearance.

b. Thickness and diameter

The thickness and diameter of the formulations were used to determine the uniformity of size and shape of the tablets. From the results it was found that the thickness of the tablet in all formulation was 3.8-4mm and the diameter of the tablet in all formulation was 8mm.The results indicated that all the formulations had uniform size and shape. The results were shown in **Table 4A**.

c. Hardness

The hardness of the tablets was used to determine the resistance capacity of the tablets to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage. The hardness of the tablets of all the formulations was found to be in the range of 3.53-3.73 kg/cm^2. The result indicated that all the tablets had a good mechanical strength. The results of the hardness for all the formulations were shown in **Table 4A.**

d. Weight variation test

The weight variation test was used to ensure the uniformity of the tablet in all formulations. The weight of all the tablets from each formulation was in the range from 198.51 mg to 200.96 mg. It was found all the tablets passed weight variation test, as the percentage weight variation was within the acceptable limits of 7.5%. The results were shown in **Table 4A**.

e. Friability test

Friability test was measured to ensure the mechanical strength of tablet. The results showed that the friability of all the formulation ranged from 0.54% to 0.76%. Friability of all the formulation was lesser than 1

% which indicated the tablets had a good mechanical resistance. The results were shown in **Table 4A.**

f. Uniformity of drug content

The uniformity content test was used to determine the uniform amount of active ingredient present in all formulations. The drug content in the content uniformity of all the formulations was found to be in the range of 97.60 % - 98.24%. The results indicated all the formulations were within the acceptable limits as per USP limits. The results were shown in **Table 4A**.

g. *In vitro* drug release study

The dissolution profile range in 30 minutes was 62.03% to 98.31% **(**Table 5A and 5B**).** The drug release was found to be comparatively less in formulation containing natural superdisintegrant (hibiscus leaves mucilage). The maximum dissolution drug release rate was observed with the formulation containing crospovidone (10mg) as a synthetic superdisintegrants.**(FIG. 12A, 12B, 12C and 12D)**

This study indicated that synthetic superdisintegrants produce the better drug release rate compared to natural superdisintegrants . the formulaion containing crospovidone (5%) was to show dissolution in 30minutes of dissolution study produced 98.31% which compiled with WHO guideline. Many factors contributed for faster drug release rate such as rapid disintegration and increased wettability. Among the 12 formulations the formulation 5 (F5) was selected, as a best formulation because of its desirable character of low disintegration time, highest drug release, high water absorption rate and short wetting time.

h. *In vitro* disintegration time

The *in-vitro* disintegration time was determined by disintegration test apparatus. The results were shown in **Table 4B.** Formulations F1, F2,

F3, F4, F5, F6, F7, F8, F9, F10, F11 and F12 showed the disintegration time 52.03, 49.53, 55.46, 42.73, 39.7, 44.3, 61.73, 63.86, 68.26, 65.43, 70.43 and 71.26 seconds respectively. It was observed that Formulation F5containing Crospovidone (5%) disintegrated rapidly in a short time (39.7seconds). The results of disintegration of all the tablets were found to be lesser than 180 seconds. So all the formulation satisfied the criteria of fast dissolving tablets.

i. Water absorption ratio

The water absorption ratio test was used to ensure the capacity of the superdisintegrant and the diluent to absorb the water. The results of water absorption ratio of all the formulation were shown in **Table 4B**.

Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11 and F12 showed the water absorption ratio 58.81%, 61.51%, 70.06%, 81.13%, 84.87%, 79.99%, 61.32%, 55.39%, 59.87%, 61.17%, 58.46% and 59.65% respectively. The results showed that as concentration of superdisintegrant increased water absorption ratio was also increased. Formulation F5 containing crospovidone (5%) as showed highest water absorption ratio (84.87%) when compared to other formulations.

The reason for high water absorption ratio for F5 formulation containing Crospovidone quickly wicks water in to the tablet to generate volume expansion. Crospovidone uses combination of swelling and wicking.

j. Wetting time

Wetting time of the tablet was used to assess the capacity of the tablets to disintegrate by swelling in water. All the formulations showed quick wetting, this may be due to ability to swelling and also capacity of absorption of water. The results of wetting time of all the formulations were shown in **Table 4B**.

The formulationsF1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11 and F12 showed the wetting time, 57.3, 56.5, 61.83, 48.2, 47.3, 51.4,

73.63, 72.43, 78.4, 74.2, 81.56 and 83.3 seconds respectively. The results indicated that the concentration of superdisintegrant influenced the wetting time. Formulation F5 containing crospovidone (5%) showed lesser wetting time than other formulations.

This may be due to fact that superdisintegrant –Crospovidone performed its action by the combination of wicking and swelling action. Formulation F5 showed shorter wetting time. **(Debjit Bhowmik *et al.*, 2009).**

VI. EFFECT OF SYNTHETIC SUPERDISINTEGRANTS ON RELEASE PROFILE OF LEVOCETIRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS

To study the effect of synthetic superdisinegrants on release rate of levocetirizine hydrochloride orodispersible tablets, six formulations (F1 to F6) were prepared by using sodium starch glycolate and crospovidone as superdisintegrant in various concentration (2.5%, 5%, 7.5%) with mannitol used as a diluent. The formulated tablets were subjected to various quality tests and the release rates were shown in **FIG. 12A and 12B**. The dissolution data was presented in the **Table 5A**. The in vitro kinetics was presented in the **Table 6A**. The dissolution rate followed first order kinetics as the graph between log% drug unreleased Vs time were found linear. The dissolution rate of levocetirizine hydrochloride with organic diluents was found better when compared with inorganic diluents.

VII. EFFECT OF NATURAL SUPERDISINTEGRANTS ON RELEASE PROFILE OF LEVOCETIRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS

To study the effect natural superdiintegrants on release rate of levocetirizine hydrochloride orodispersible tablets, six formulations (F7 to F12) were prepared by using hibiscus leaves mucilage and plantago ovata seed mucilage as superdisintegrant in various concentration

(2.5%, 5%, 7.5%) with mannitol as a diluent. The formulated tablets were subjected to various quality tests and the release rates were shown in **FIG. 12C and 12D**. The dissolution data was presented in the **Table 5B**. The invitro kinetics was presented in the **Table 6B**. The dissolution rate followed first order kinetics as the graph between log% drug unreleased Vs time were found linear. The dissolution rate of naural superdisintegrants was found lower compared with synthetic superdisintegrants.

VIII. COMPARISION OF DISSOLUTION DATA OF LEVOCETIRIZINE HYDROCHLORIDE TABLETS CONTAINING DIFFERENT SUPERDISINTEGRANTS

The tablets prepared with crospovidone showed maximum drug release of 98.31% whereas tablets containing sodium starch glycolate, plantago ovata seed mucilage and hibiscus leaves mucilage showed maximum drug release of 90.11%, 80.43% and 67.32% respectively.

IX. SELECTION OF BEST FORMULATION

Among twelve formulations, the best was selected on the basis of lowest disintegration time, rapid drug release profile, higher water absorption ratio, short wetting time. Formulation F5 showed lowest disintegration time of 39.7 seconds, faster drug release rate of 98.31 %in 30 minutes, comparatively high water absorption ratio of 84.87% and short wetting time of 47.3 seconds. In these parameter would drive the F5 formulation as a best formulation.

X. EVALUATION OF SELECTED FORMULATION

a.Differential Scanning Calorimetry (DSC) Studies

Any possible drug polymer interaction can be studied by thermal analysis. The DSC thermogram of levocetirizine hydrochloride exhibited an sharp endothermic peak at at 218.862^{o}C, which corresponding to its

melting temperaure. The thermogram of the final best formulation of levocetirizine hydrochloride with other excipients show the existence of drug endothermic peak within the range which indicated the absence of interaction between the drug and other excipients. The DSC thermogram of pure drug and the final best formulation is presented in **FIG. 5A and 5B** .

b. Fourier Transform Infra-Red (FT-IR) Spectroscopic studies

Infrared spectra of the levocetirizine hydrochloride orodispersible tablets showed major peaks at 1739 cm^{-1}, 2947.23 cm^{-1} and 75 cm^{-1} indicated that there was no interaction between the drug and the final formulation throughout the preparation of orodispersible tablets. The result was shown in **FIG. 3J.**

c. Powder X-Ray Diffraction

The X-Ray diffracograms of Levocetirizine hydrochloride best formulation (F5) showed the characteristic peaks between 2θ of 15^{o} and 25^{o} indicated that there ws no interaction between the drug and excipients. The result was shown in **FIG. 6A and 6B.**

XI. DRUG RELEASE KINETIC MODEL

In order to describe the kinetics of the release process of drug in all formulations, equations such as zero-order and first- order rate equations were used. Zero order rate equation describes the system where the release rate is independent of the concentrations of the dissolved species. While the first- order equation describes the release from systems where dissolution rate is dependent on the concentration of the dissolving species. It is evident from **Table 6A and 6B** that the drug release process is not zero order in nature. This indicates that the dissolution rate of the drug is not independent of the amount of drug available for dissolution and diffusion from the matrix. The dissolution

data of all formulations when fitted in accordance with the first order equation it is evident that a linear relationship was obtained with 'r' (correlation coefficient) value close to unity and higher than 'r' obtained from zero order equation for all formulation (table), showing that the release is an apparent first order process. This indicates that the amount of drug released is dependent on the matrix.

The obtained from *invitro* dissolution studies were fitted to zero – order, first-order and Korsmeyer Peppas equation. The first-order plots were found to be fairly linear as indicated by their high regression values. To confirm the exact mechanism of drug release, the data were fitted according to Korsmeyer Peppas equation:

$$\mathbf{Mt/m\infty = k\ tn}$$

where mt/m∞ is fraction of drug released, k is kinetic constant, t is release time and *n* is the diffusional exponent for drug release. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of '*n*' gives an indication of the release mechanism; when *n* =1, the release rate is independent of time (zero-order) (case II transport), *n* = 0.5 for Fickian diffusion and when 0.5 < *n* <1.0, diffusion and non-Fickian transport are implicated. Lastly, when *n* > 1.0 super case II transport is apparent. '*n*' is the slope value of log mt/m∞ versus log time curve**.** Slope values (*n* > 1.0) suggest that the release of cilnidipine from orodispersible tablets followed Supercase-II transport suggesting that more than one mechanism may be involved in the release kinetics. The results were shown in **table 6A and 6B.**

XII. STABILITY STUDIES

The formulations F5 was selected for stability studies on the basis of their high cumulative % drug release and also results of *in vitro* disintegration time and wetting time. The stability studies carried out at

25^{O}C (room temperature) and 40^{O}C/75%RH for the best formulations up to 30 days. In 15 day time interval, the tablets were analyzed for hardness, drug content uniformity, *invitro* disintegration time, % drug release up to 30 days. The formulation showed not much variation in any parameter. The results are tabulated in **Table 7A and 7B.** From these results it was concluded that, formulation F5 (crospovidone 5%) was stable and retained its original properties.

TABLE 1: CALIBRATION OF LEVOCETRIZINE HYDROCHLORIDE WITH PHOSPHATE BUFFER pH 6.8

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE ±SD
1	4	0.134 ± 0.015
2	8	0.229 ± 0.0013
3	12	0.341 ± 0.006
4	16	0.456 ± 0.009
5	20	0.569 ± 0.010
6	24	0.685 ± 0.006
7	28	0.810 ± 0.020
8	32	0.912 ± 0.006

N= 3 * REGRESSION VALUE =0.99928±0.0003

TABLE 2 A: LEVOCETRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS (F1 TO F6)

INGREDIENTS	F1	F2	F3	F4	F5	F6
Levocetrizine hydrochloride (Small)	10	10	10	10	10	10
Microcrystalline Cellulose	30	30	30	30	30	30
Sodium starch Glycolate	5	10	15	-	-	-
Crospovidone	-	-	-	5	10	15
Mannitol	148	143	138	148	143	138
Saccharin Sodium	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1
Talc	2	2	2	2	2	2

TABLE 2 B: LEVOCETRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS (F7 TO F12)

INGREDIENTS	F7	F8	F9	F10	F11	F12
Levocetrizine hydrochloride	10	10	10	10	10	10
Microcrystalline Cellulose	30	30	30	30	30	30
Hibiscus leaves mucilage	5	10	15	-	-	-
Plantago ovata seeds mucilage	-	-	-	5	10	15
Mannitol	148	143	138	148	143	138
Saccharin Sodium	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1
Talc	2	2	2	2	2	2

TABLE 3: PRE COMPRESSION EVALUATION STUDY FOR LEVOCETRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS FORMULATIONS

Formulation code	Angle of repose	Bulk density	Tapped density	Percentage of compressibility	Hausner's Ratio
F1	28.92±0.718	0.78±0.015	0.85±0.024	8.693±0.880	1.095±0.104
F2	30.02±0.392	0.78±0.010	0.87±0.007	9.611±0.639	1.100±0.007
F3	30.86±0.704	0.77±0.015	0.86±0.006	9.565±1.718	1.115±0.014
F4	30.04±0.465	0.77±0.015	0.86±0.006	11.128±3.023	1.126±0.038
F5	27.29±0.801	0.78±0.010	0.86±0.012	9.201±0.098	1.101±0.001
F6	28.58±0.402	0.77±0.015	0.87±0.019	11.211±0.768	1.120±0.009
F7`	34.32±0.573	0.67±0.012	0.74±0.019	10.351±0.761	1.115±0.009
F8	32.02±1.103	0.65±0.015	0.75±0.019	10.483±0.678	1.117±0.008
F9	31.31±1.009	0.68±0.018	0.75±0.009	11.555±1.367	1.130±0.017
F10	30.86±0.704	0.75±0.014	0.86±0.018	11.847±1.869	1.134±0.024
F11	33.21±0.903	0.74±0.013	0.83±0.006	12.985±1.129	1.148±0.015
F12	33.04±1.518	0.75±0.018	0.83±0.023	11.154±0.285	1.125±0.004

TABLE 4A: POST COMPRESSION EVALUATION STUDY FOR LEVOCETRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS FORMULATION

F.code	Weight uniformity test ± SD	Drug content in percentage ± SD	Hardness(kg / cm^2) ± SD	Thickness (mm) ± SD	Friability ±SD
F1	198.51±0.341	97.60±0.805	3.56±0.115	3.96±0.057	0.630±0.043
F2	198.68±0.326	98.10±0.254	3.7±0.1	4±0.1	0.63±0.014
F3	199.01±0.577	97.81±0.44	3.7±0.1	4.06±0.057	0.58±0.126
F4	199.01±0.459	98.24±0.435	3.66±0.152	3.96±0.057	0.55±0.024
F5	199.07±0.610	98.24±0.435	3.53±0.057	4±0.1	0.55±0.015
F6	199.28±0.583	98.1±0.502	3.6±0.1	4.03±0.152	0.54±0.039
F7	200.19±0.468	98.1±0.502	3.7±0.1	3.93±0.057	0.66±0.045
F8	200.96±0.482	98.24±0.435	3.66±0.115	3.9±0.1	0.68±0.010
F9	199.96±1.531	97.66±0.906	3.66±0.057	3.96±0.057	0.74±0.035
F10	200.19±0.458	97.81±0.44	3.7±0.1	3.93±0.152	0.76±0.011
F11	200.37±0.483	98.24±0.435	3.63±0.152	3.9±0.1	0.70±0.019
F12	199.55±0.704	98.10±0.254	3.73±0.057	3.83±0.057	0.67±0.063

TABLE 4B: POST COMPRESSION EVALUATION STUDY FOR LEVOCETIRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS

FORMULATION CODE	Disintegration time in sec ±SD	Water Absorption ratio in % ± SD	Wetting Time in sec ± SD
F1	52.03±1.250	58.81±0.712	57.3±1.951
F2	49.53±0.737	61.51±0.793	56.5±1.752
F3	55.46±1.083	70.06±1.582	61.83±1.550
F4	42.46±0.757	81.13±2.041	48.2±0.6
F5	39.7±0.458	84.87±2.914	47.3±0.953
F6	44.3±0.818	79.99±3.208	51.4±1.081
F7	61.73±2.247	61.3±3.746	73.63±3.156
F8	63.86±1.222	55.39±1.030	72.43±2.020
F9	68.26±2.550	59.87±1.736	78.4±4.150
F10	65.43±1.205	61.17±2.540	74.2±1.552
F11	70.43±1.724	58.46±2.15	81.56±2.909
F12	71.26±1.890	59.65±0.905	83.3±3.051

TABLE 5A: *Invitro* RELEASE PROFILE OF LEVOCETRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS

FORMULATION CODE	5TH MINUTE	10TH MINUTE	15TH MINUTE	20TH MINUTE	25TH MINUTE	30TH MINUTE
F1	77.23 ± 0.446	78.94 ± 0.258	80.73 ± 0.682	82.22 ± 1.182	84.01 ± 1.182	85.94 ± 0.930
F2	77.97 ± 0.257	80.13 ± 0.258	82.52 ± 0.516	85.05 ± 0.258	87.73 ± 0.258	90.11 ± 0.6826
F3	75.14 ± 0.681	77.30 ± 0.893	78.94 ± 0.930	80.88 ± 1.182	82.67 ± 0.893	84.31 ± 0.516
F4	81.84 ± 0.681	84.31 ± 0.930	86.69 ± 0.774	89.07 ± 1.032	91.60 ±1.182	94.14 ± 0.930
F5	84.82 ± 0.446	87.43 ± 0.682	90.11 ± 0.682	92.50 ± 0.446	95.33 ± 0.516	98.31 ± 0.446
F6	81.72 ± 0.406	84.01 ± 0.446	86.24 ± 0.774	88.92 ± 1.182	91.60 ± 1.182	94.43 ± 0.930

TABLE 5B: *IN-VITRO* RELEASE PROFILE OF LECOCETIRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS

F.CODE	5^{TH} MINUTE	10^{TH} MINUTE	15^{TH} MINUTE	20^{TH} MINUTE	25^{TH} MINUTE	30^{TH} MINUTE
F7	50.03 ±1.975	53.17 ±0.446	55.11 ±0.258	57.34 ±0.682	59.73 ±0.930	62.11 ±0.895
F8	54.46 ±0.446	56.60 ±0.258	59.43 ±0.446	61.37 ±0.930	64.49 ±1.365	67.32 ±1.436
F9	51.488 ±0.681	53.17 ±0.893	55.71 ±1.569	57.79 ±1.569	66.03 ±1.124	62.03 ±1.914
F10	66.66 ±0.681	69.11 ±0.930	71.94 ±1.182	74.47 ±1.365	76.86 ±1.340	79.245 ±1.365
F11	69.79 ±0.681	72.24 ±0.930	74.03 ±0.258	76.56 ±0.258	78.50 ±0.258	80.43 ±0.446
F12	68.450 ±0.681	70.90 ±1.124	73.13 ±1.56	75.52 ±2.047	77.45 ±1.806	79.39 ±1.860

TABLE 6A : *IN-VITRO* RELEASE KINETICS DATA OF LEVOCETIRIZINE HYDROCHLORIDE

Formulation code	Zero order		First order		Higuchi		Korsmeyer Peppas		Hixson Crowell	
	r^2	K^0 (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_H($h^{-1/2}$)	r^2	n	r^2	K_{HC}($h^{-1/3}$)
F1	0.468	1.961	0.619	-0.021	0.745	14.21	0.778	0.598	0.659	-0.005
F2	0.505	2.105	0.733	-0.026	0.775	14.99	0.791	0.602	0.788	-0.006
F3	0.476	1.939	0.623	-0.02	0.752	14.00	0.782	0.585	0.660	-0,005
F4	0.498	2.190	0.781	-0.032	0.770	15.64	0.788	0.614	0.850	-0.009
F5	0.505	2.293	0.873	-0.047	0.775	16.32	0.789	0.626	0.863	-0.017
F6	0.503	2.199	0.784	-0.033	0.733	15.67	0.789	0.614	0.859	-0.009

TABLE 6B : *IN-VITRO* RELEASE KINETICS DATA OF LEVOCETIRIZINE HYDROCHLORIDE

Formulation code	Zero order		First order		Higuchi		Korsmeyer Peppas		Hixson Crowell	
	r^2	K^0 (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_H($h^{-1/2}$)	r^2	n	r^2	K_{HC}($h^{-1/3}$)
F7	0.560	1.499	0.656	-0.010	0.820	10.42	0.829	0.502	0.674	-0.002
F8	0.562	1.619	0.677	-0.012	0.820	11.24	0.824	0.522	0.698	-0.002
F9	0.543	1.484	0.640	-0.010	0.806	10.39	0.820	0.501	0.657	-0.002
F10	0.529	1.882	0.687	-0.017	0.795	13.26	0.805	0.568	0.720	-0.004
F11	0.500	1.878	0.643	-0.017	0.772	13.41	0.793	0.572	0.675	-0.004
F12	0.506	1.862	0.648	-0.017	0.777	13.26	0.796	0.569	0.680	-0.004

TABLE 7A : STABILITY FOR THE BEST FORMULATION (F5)

TEMPERATURE	DAYS	DRUG CONTENT (%)	HARDNESS IN kg / cm^2	DISINTEGRATION TIME	DRUG RELEASE (%)
25º C	15	98.19	3.65	40.6	98.16
	30	98.1	3.7	41.2	97.12
40º C / 75 % RH	15	97.8	3.8	41.8	96.97
	30	97.66	3.84	42.3	95.18

TABLE 7B :*In vitro* RELEASE OF STABILITY STUDIES FOR THE BEST FORMULATION (F5)

TIME IN MINS	CONTROL	25º C		40º C / 75 % RH	
		15TH DAY	30TH DAY	15TH DAY	30TH DAY
5	84.82 ±0.446	85.89 ± 1.907	83.92±1.609	82.72 ± 0.406	81.72 ±0.406
10	87.43 ±0.682	88.48 ± 2.047	86.39±1.806	84.57 ± 0.636	84.57 ±0.636
15	90.11 ±0.682	90.864 ±1.569	88.48±2.047	86.544±0.258	86.54 ±0.258
20	92.50 ±0.446	93.39 ±1.947	91.46 1.806	90.11±0.682	89.07 ± 0.930
25	95.33 ±0.516	96.07 ±1.611	94.58±1.806	94.43±1.290	91.758 ±0.930
30	98.31 ±0.446	98.16±0.258	97.12±1.691	96.97±1.154	95.18 ±0.446

FIG.1: DETERMINATION OF λmax OF LEVOCETIRIZINE HYDROCHLORIDE

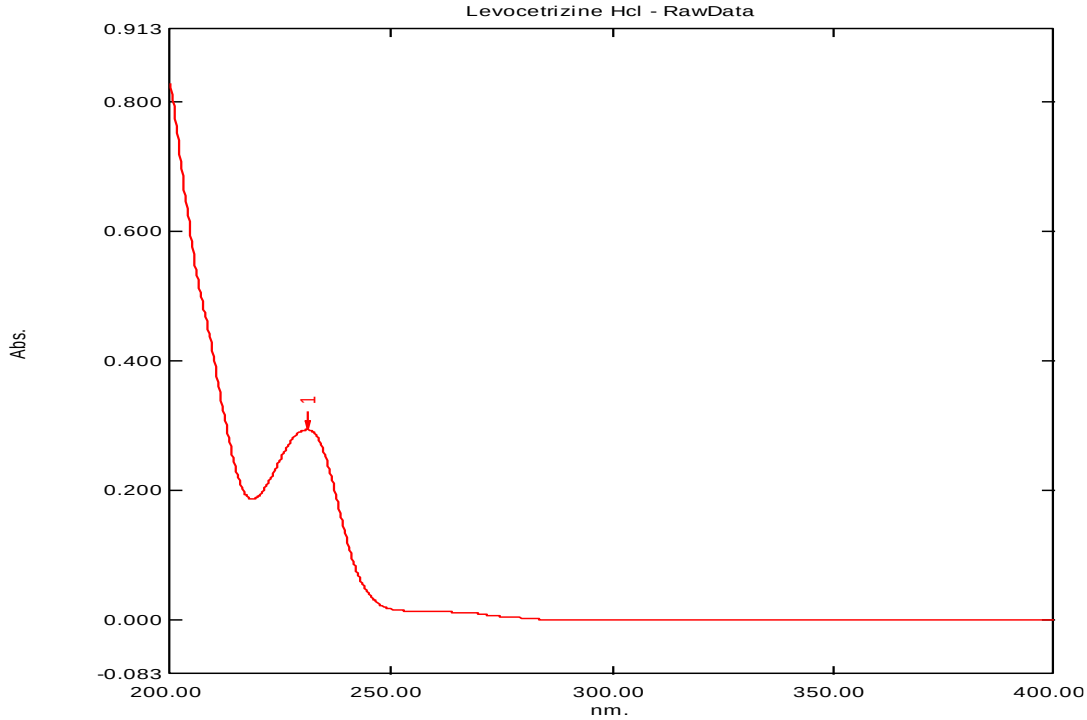


FIG.2: CALIBRATION OF LEVOCETIRIZINE HYDROCHLORIDE

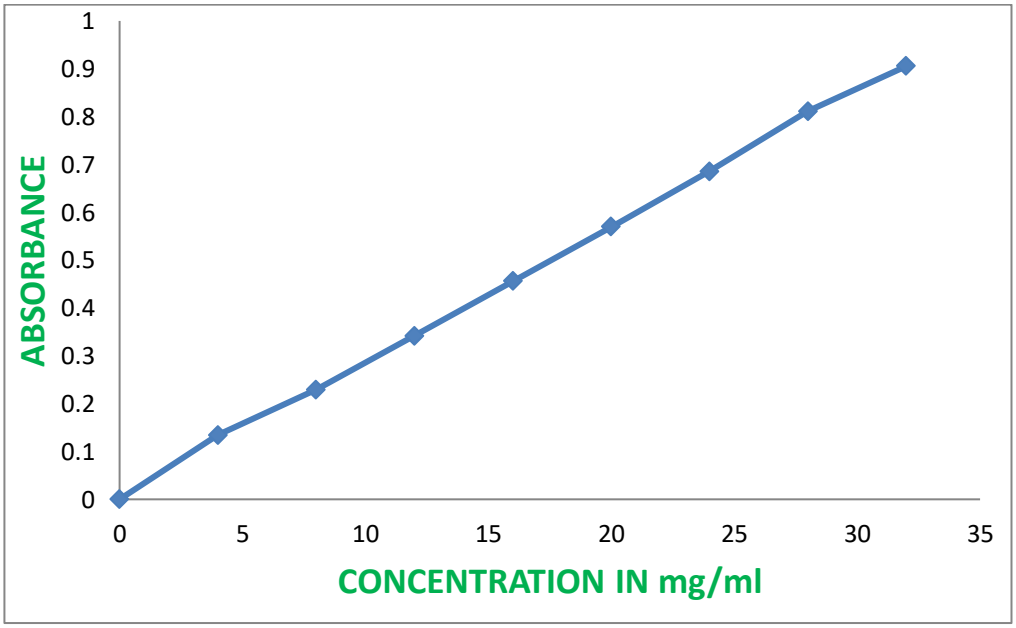


FIG.3A : FT-IR SPECTRUM – LEVOCETIRIZINE HYDROCHLORIDE

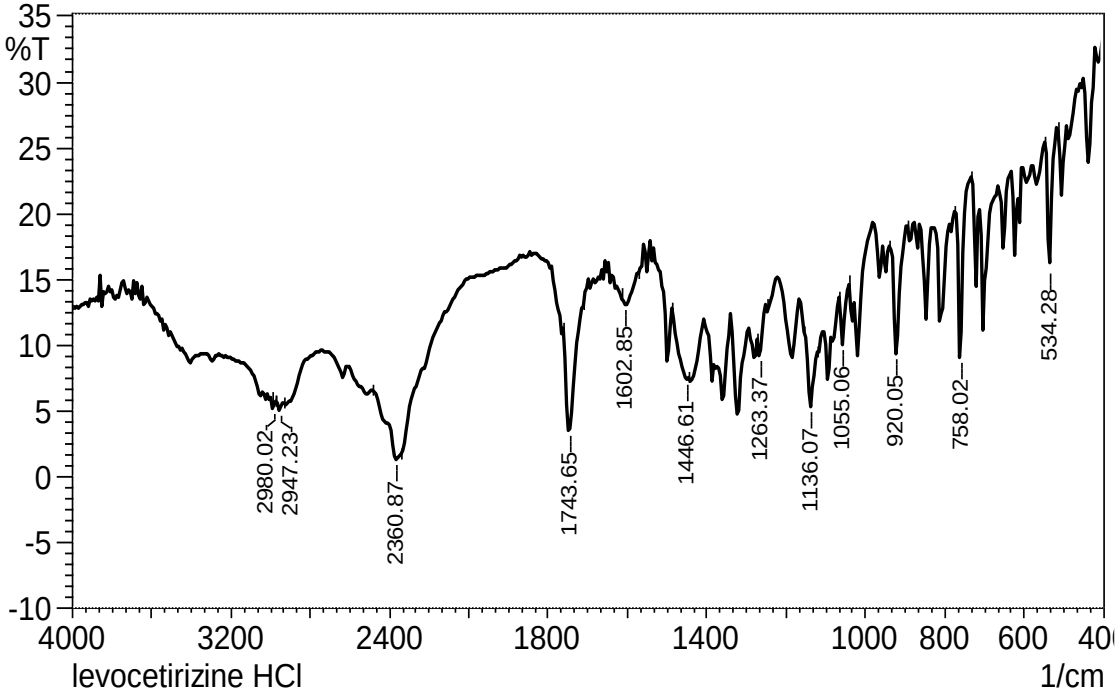


FIG.3B : FT-IR SPECTRUM - CROSSPOVIDONE

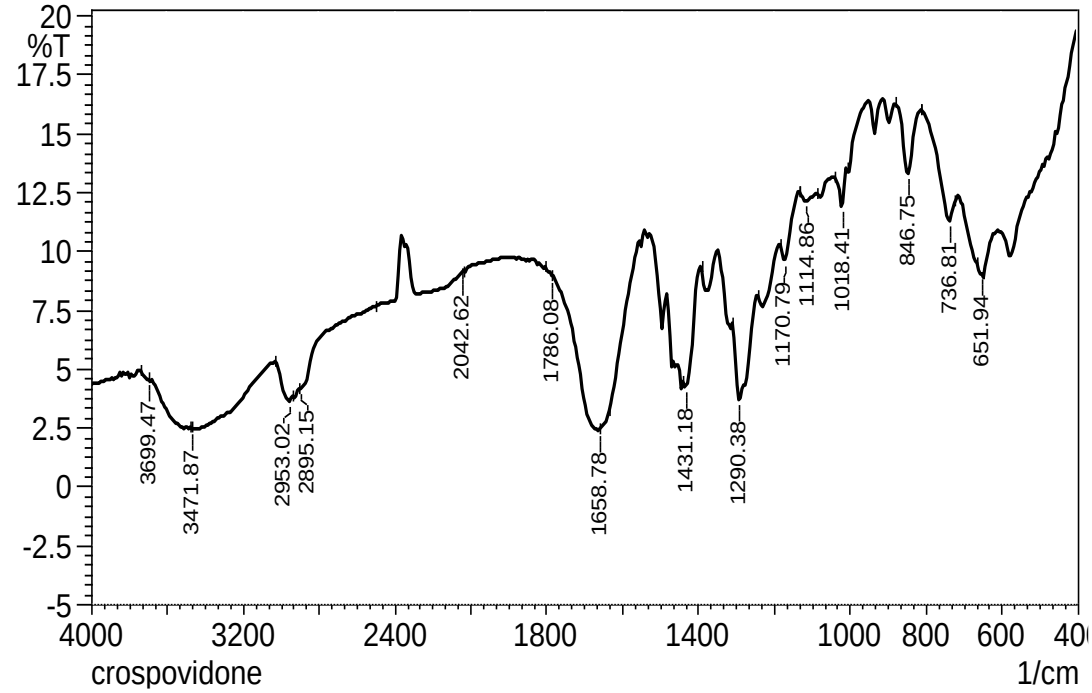


FIG.3C : FT-IR SPECTRUM – SODIUM STARCH GLYCOLATE

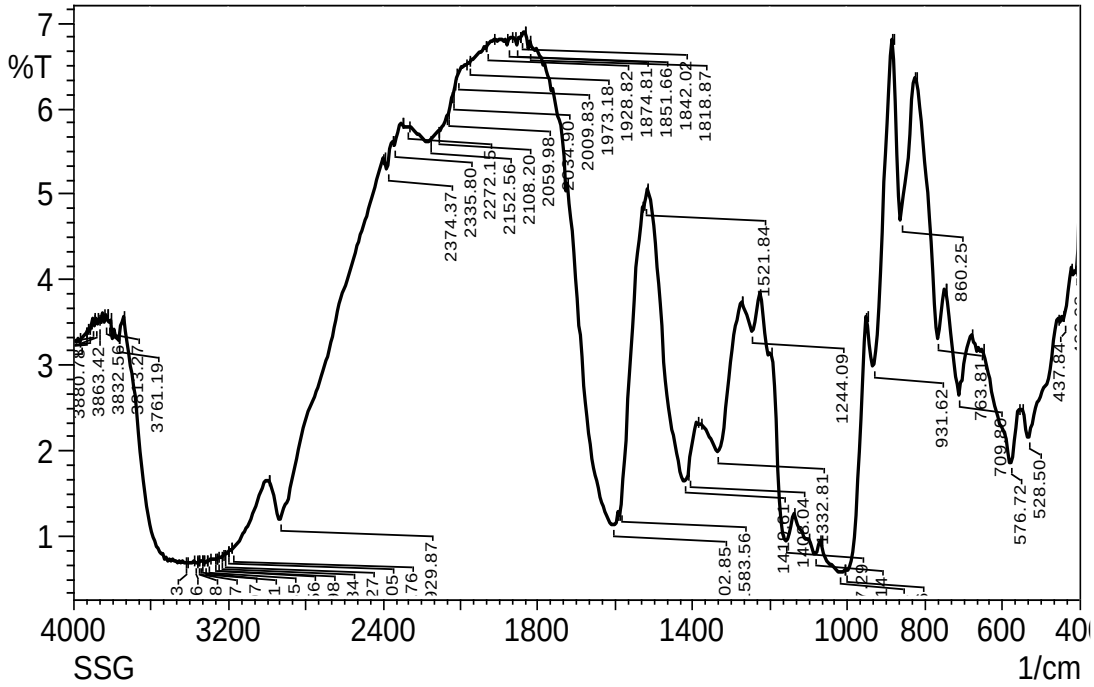


FIG.3D : FT-IR SPECTRUM - MICROCRYSTALLINE CELLULOSE

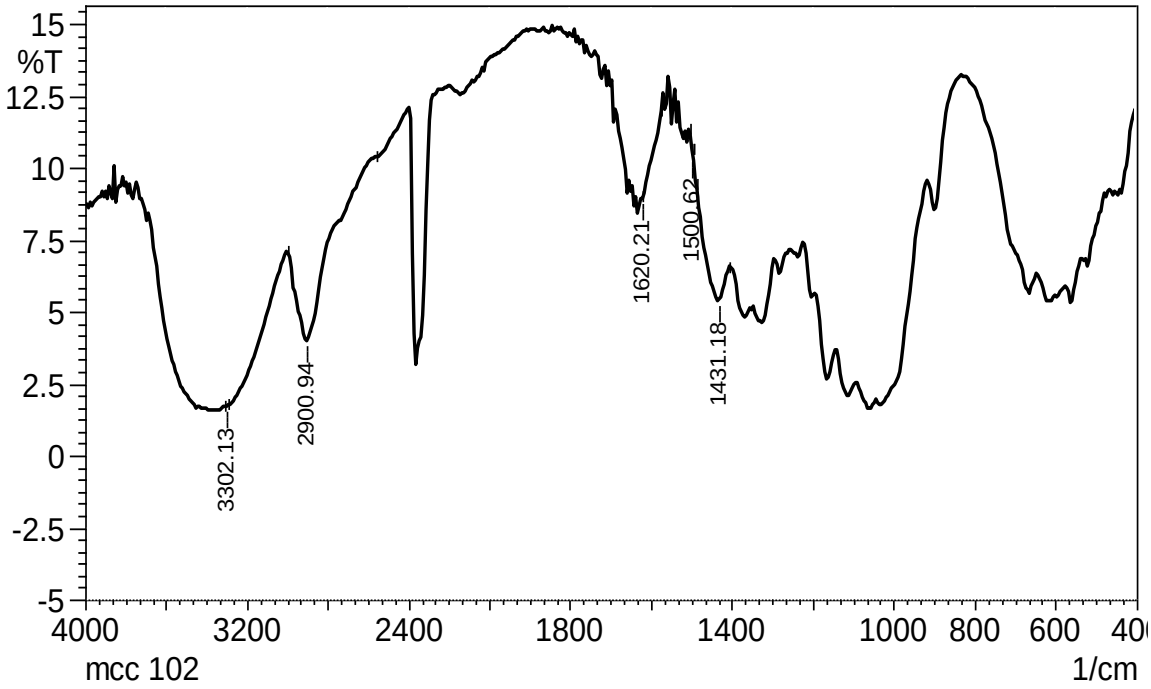


FIG.3E :FT-IR SPECTRUM – AEROSIL

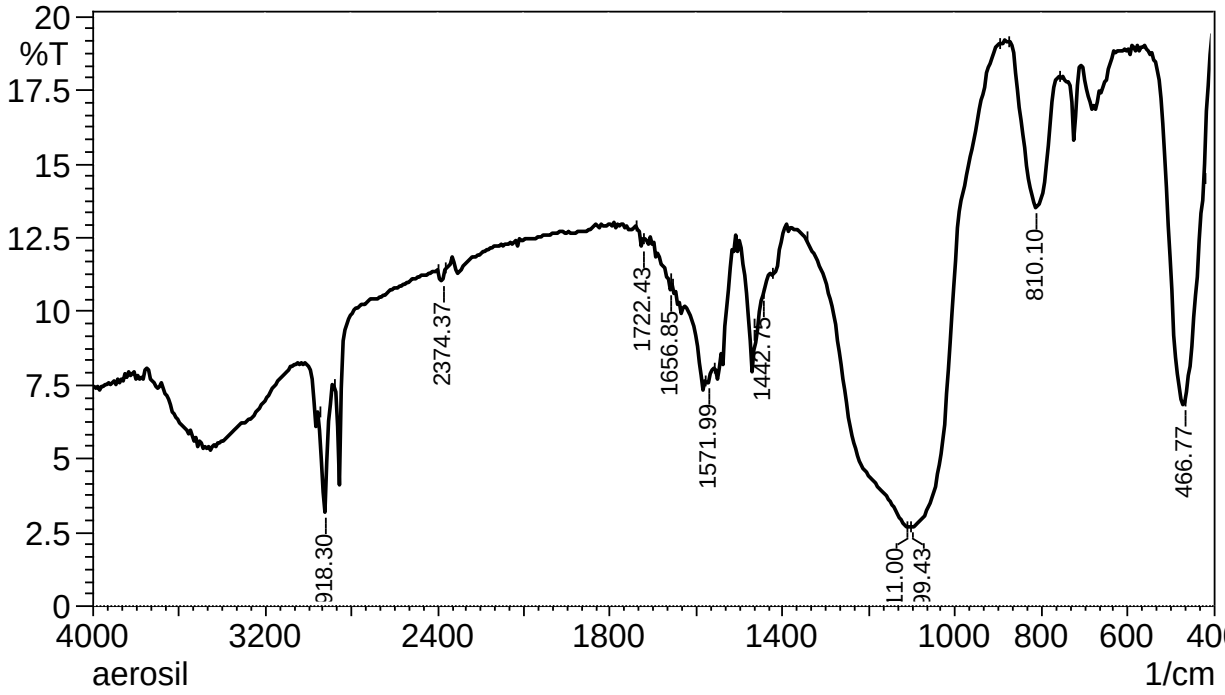


FIG.3F : FT-IR SPECTRUM – DRUG WITH CROSPOVIDONE

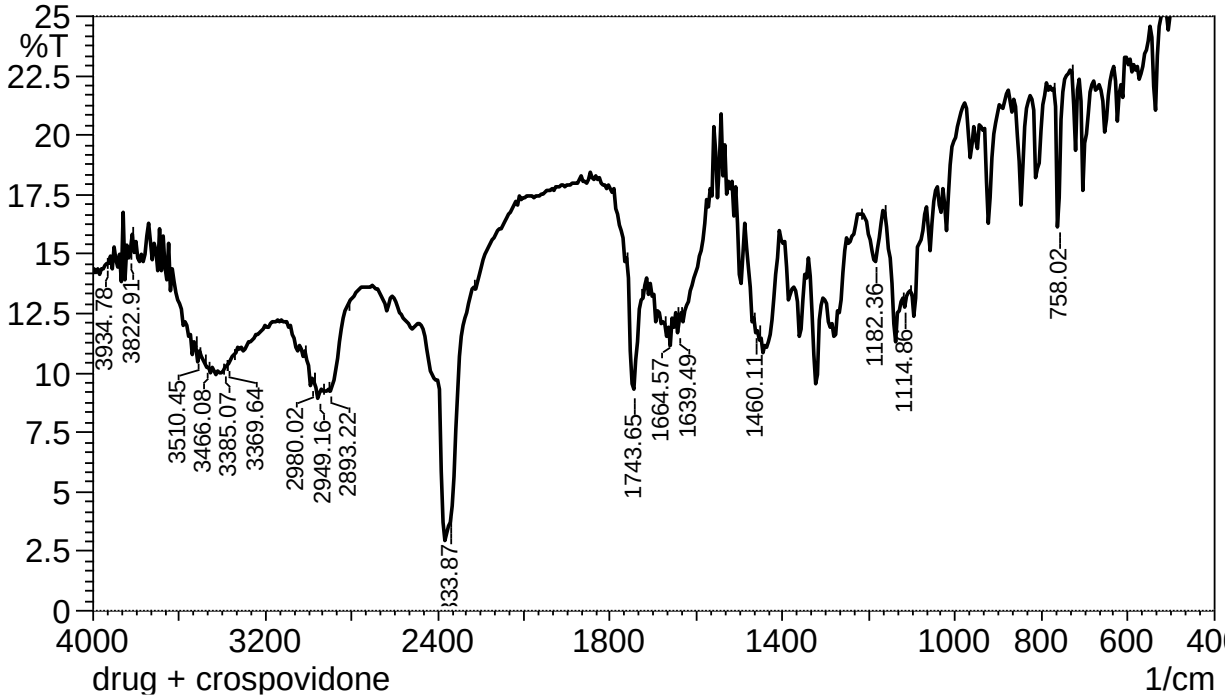


FIG.3G : FT-IR SPECTRUM – DRUG WITH SODIUM STARCH GLYCOLATE

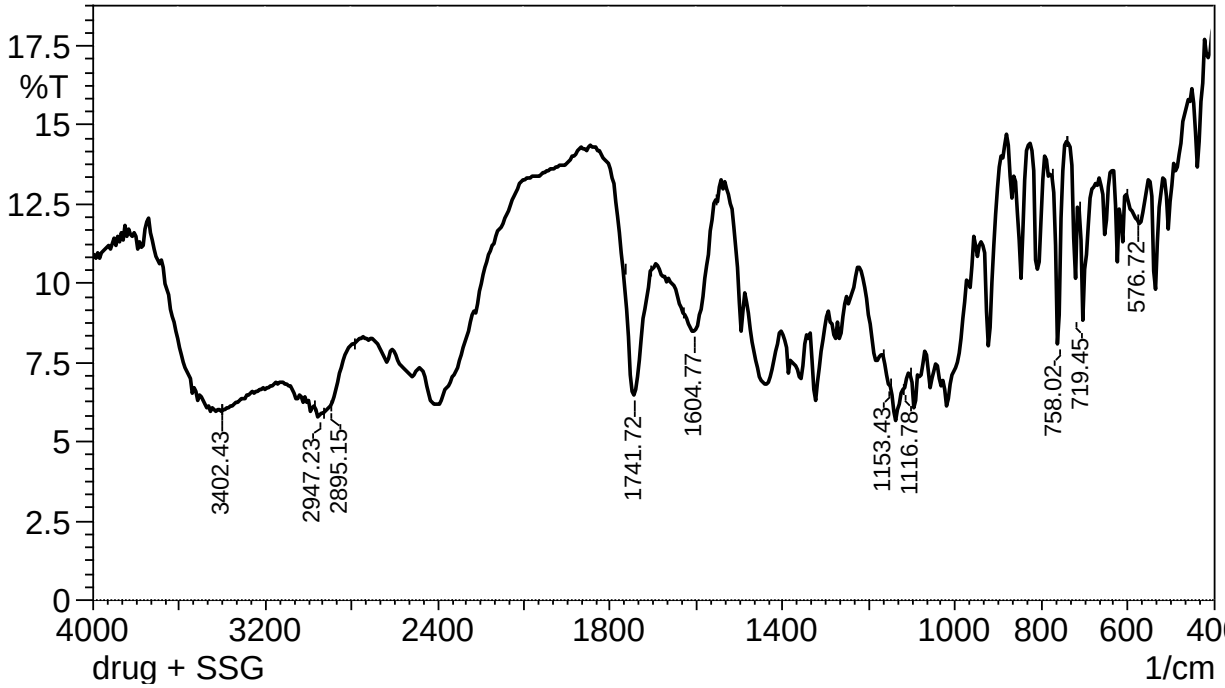


FIG.3H : FT-T-IR SPECTRUM – DRUG WITH HIBISCUS LEAVES DRIED MUCILAGE

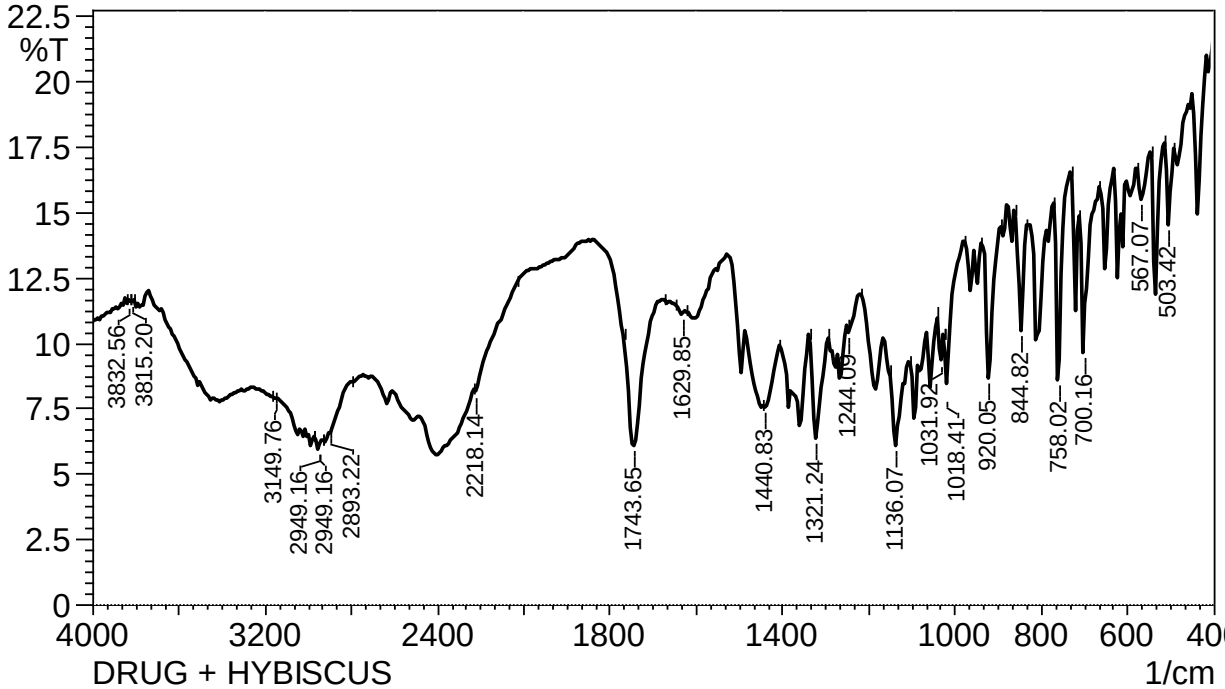


FIG.3I : FT-IR SPECTRUM – DRUG WITH PLANAGO OVATA DRIED MUCILAGE

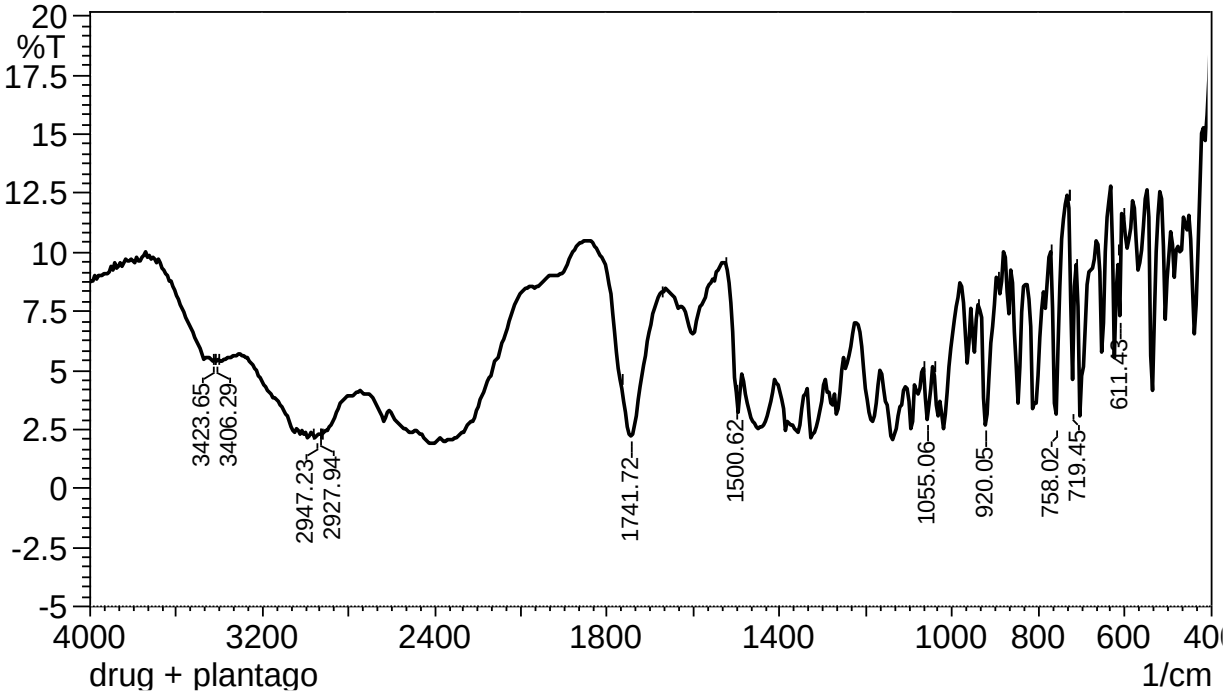


FIG.3J : FT-IR SPECTRUM – BEST FORMULATION

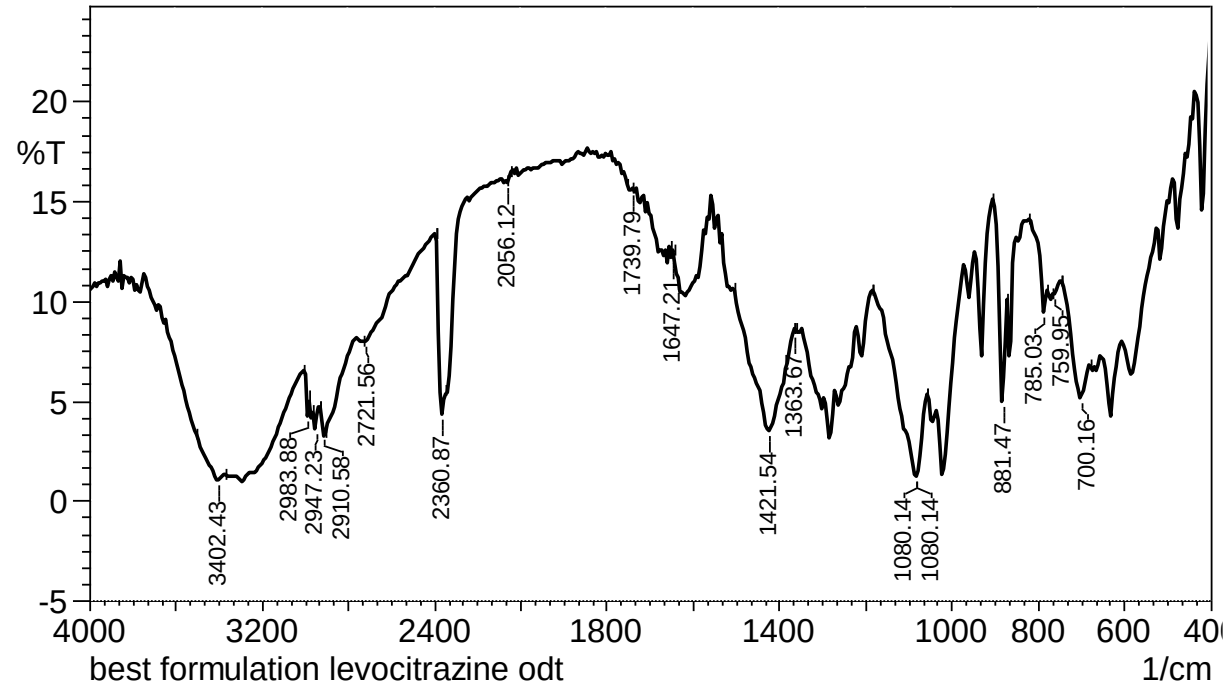


FIG.4A : XRD OF PURE DRUG

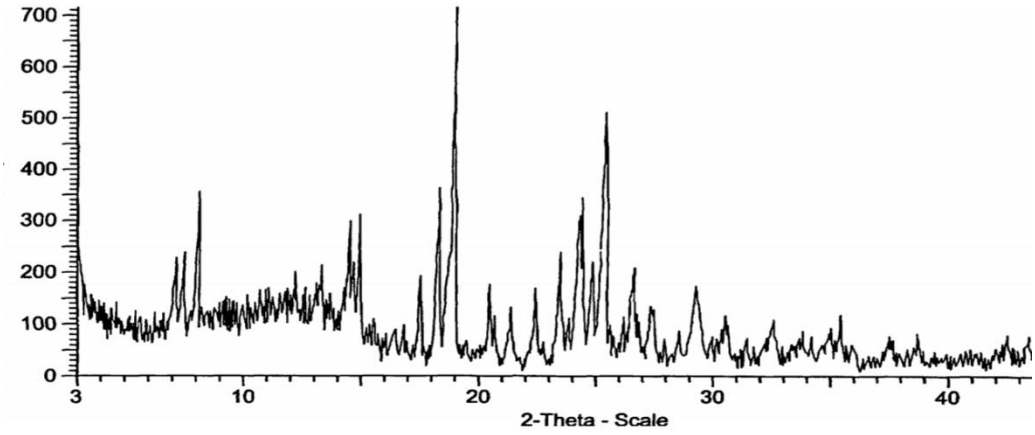


FIG.4B : XRD OF BEST FORMULATION

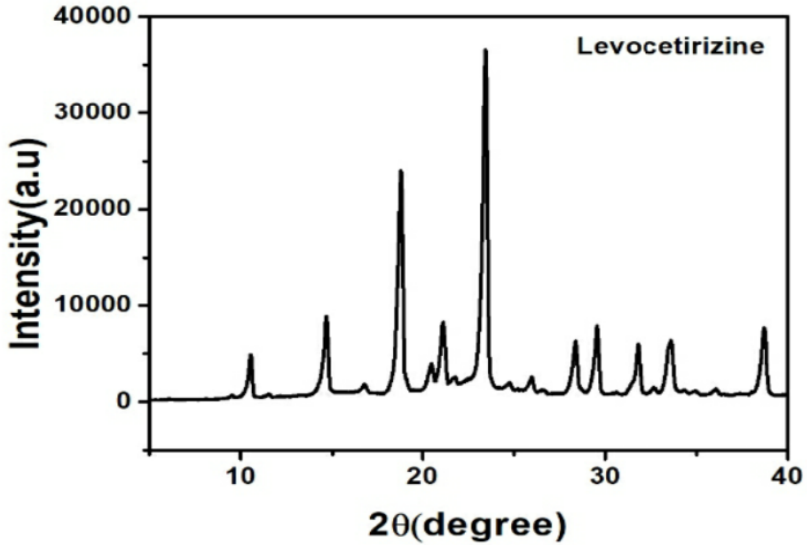


FIG 5A : DSC OF PURE DRUG

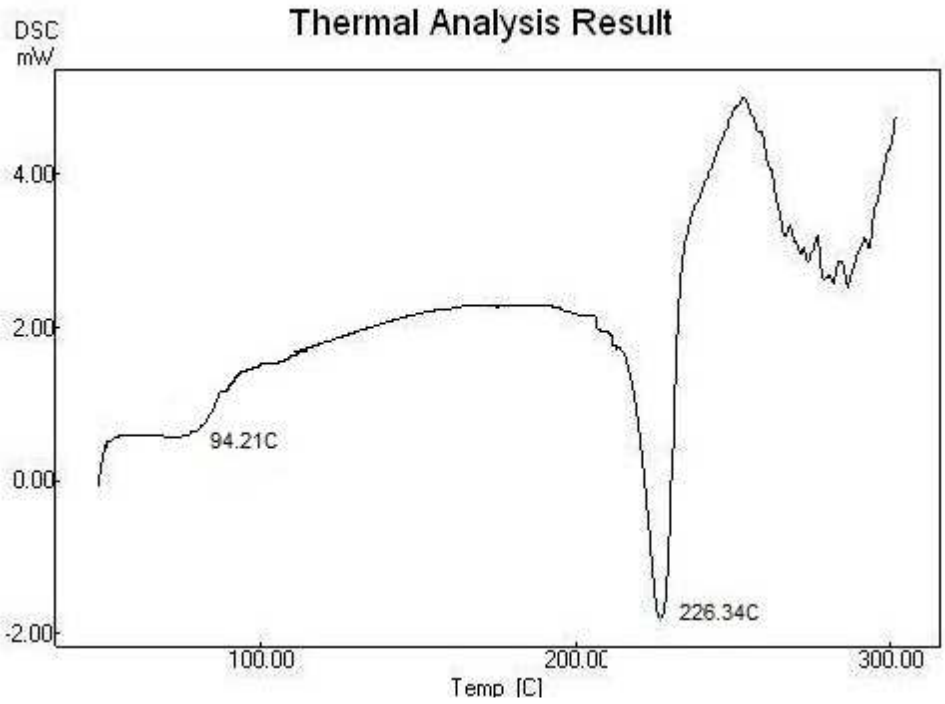


FIG.5 B: DSC OF BEST FORMULATION (F5)

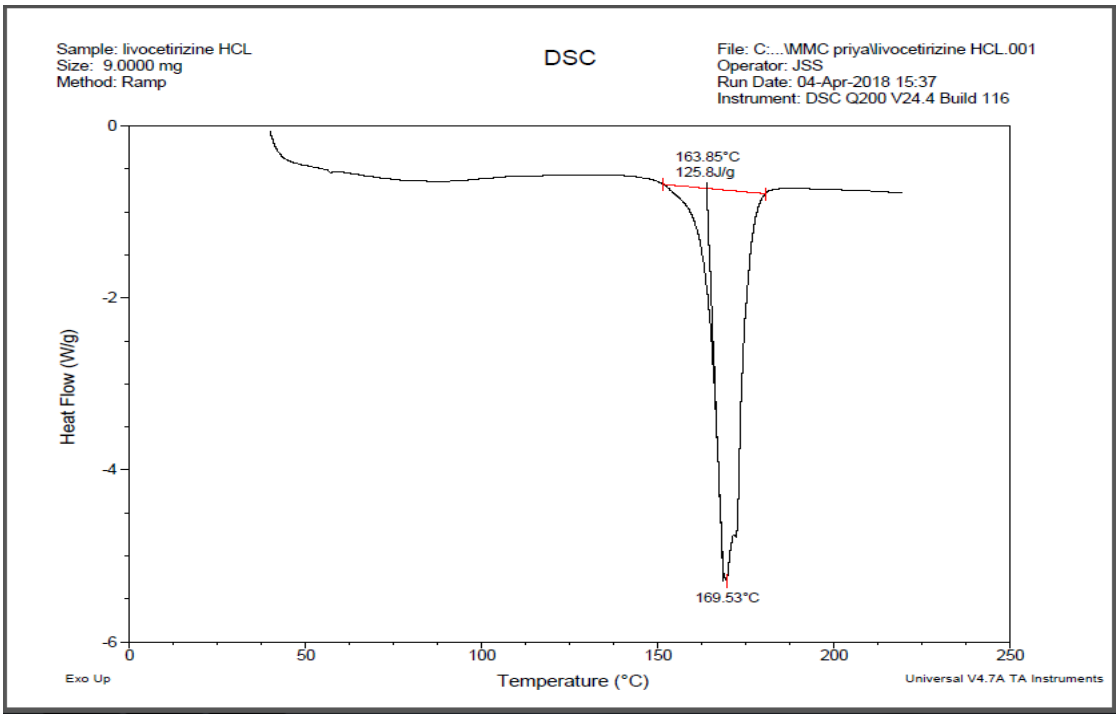


FIG.6 : ANGLE OF REPOSE OF ALL FORMULATIONS (F1-F12)

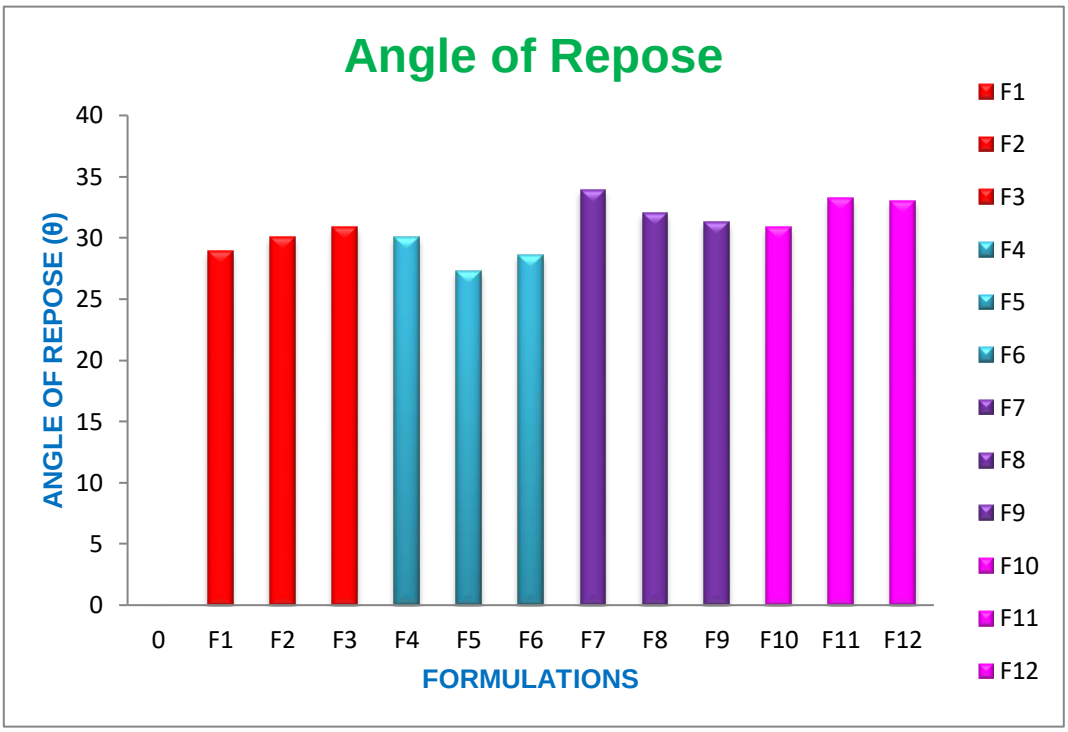


FIG.7 : BULK DENSITY OF ALL FORMULATIONS (F1-F12)

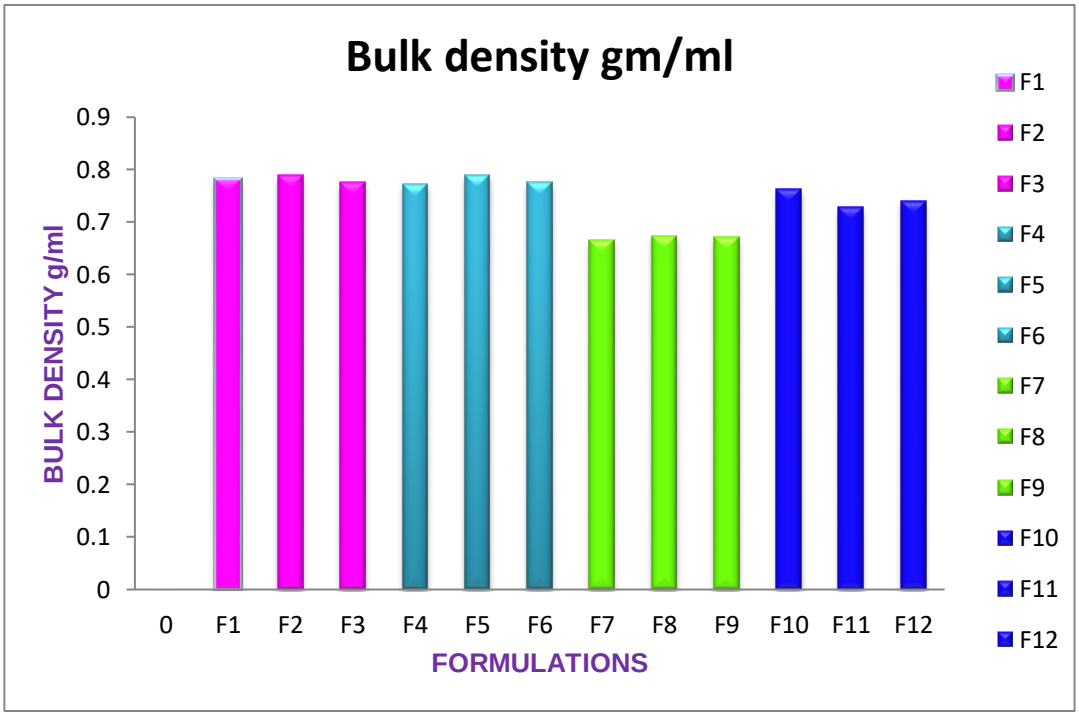


FIG.8 : TAPPED DENSITY OF ALL FORMULATIONS (F1-F12)

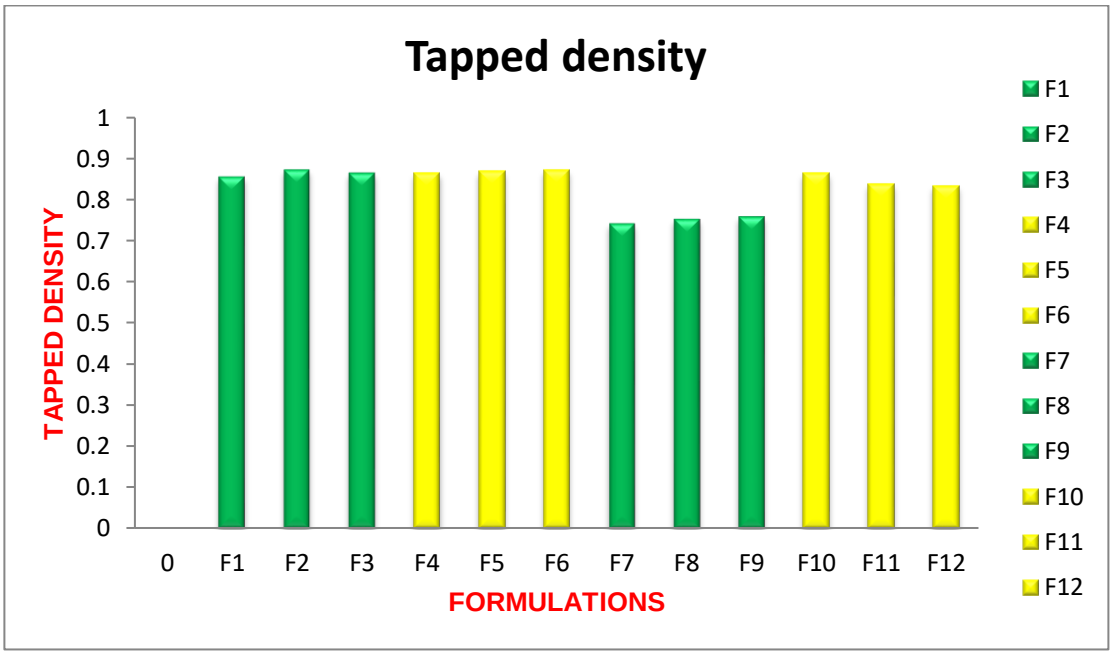


FIG.9 : COMPRESSIBILITY INDEX OF ALL FORMULATIONS (F1-F12)

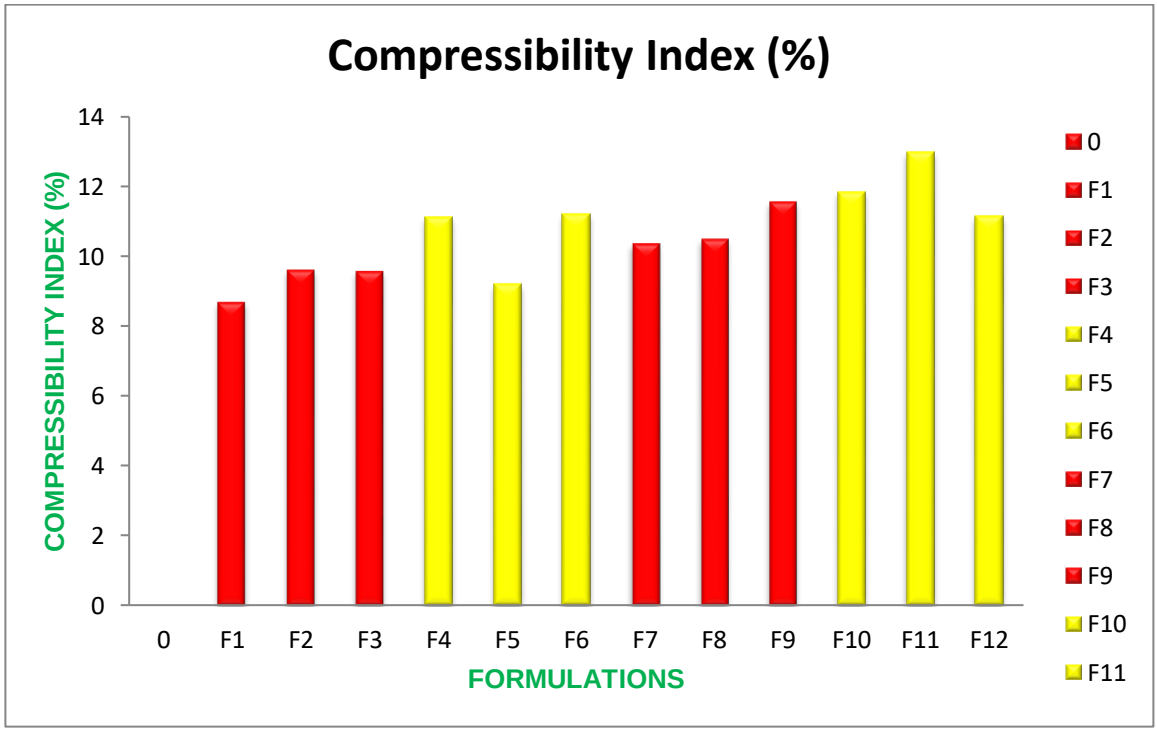


FIG. 10 : HAUSNER'S RATIO OF ALL FORMULATIONS (F1-F12)

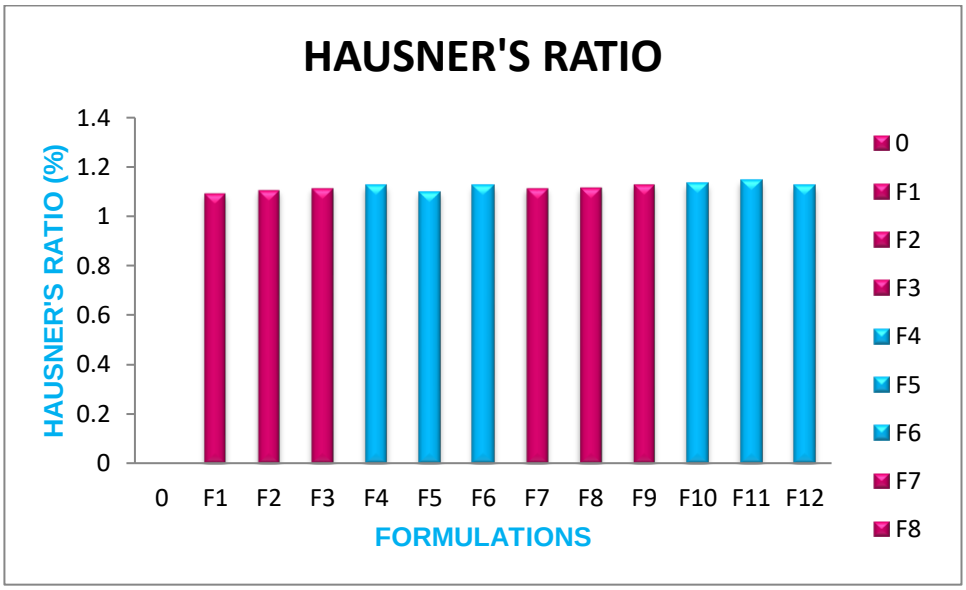


FIG.11 : DRUG CONTENT FOR ALL FORMULATIONS (F1-F12)

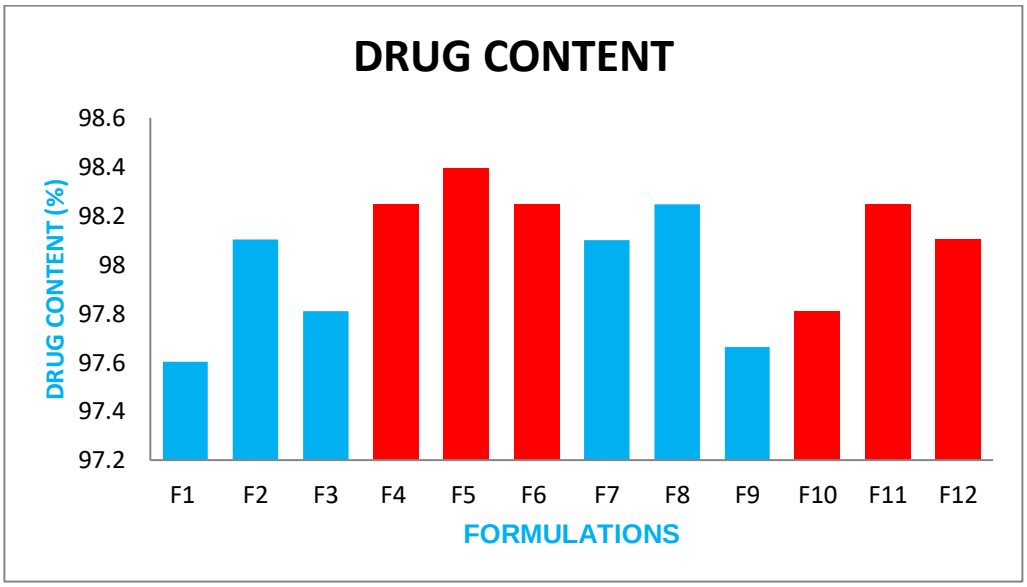


FIG.12A : *IN-VITRO* RELEASE OF LEVOCETIRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS (F1-F3)

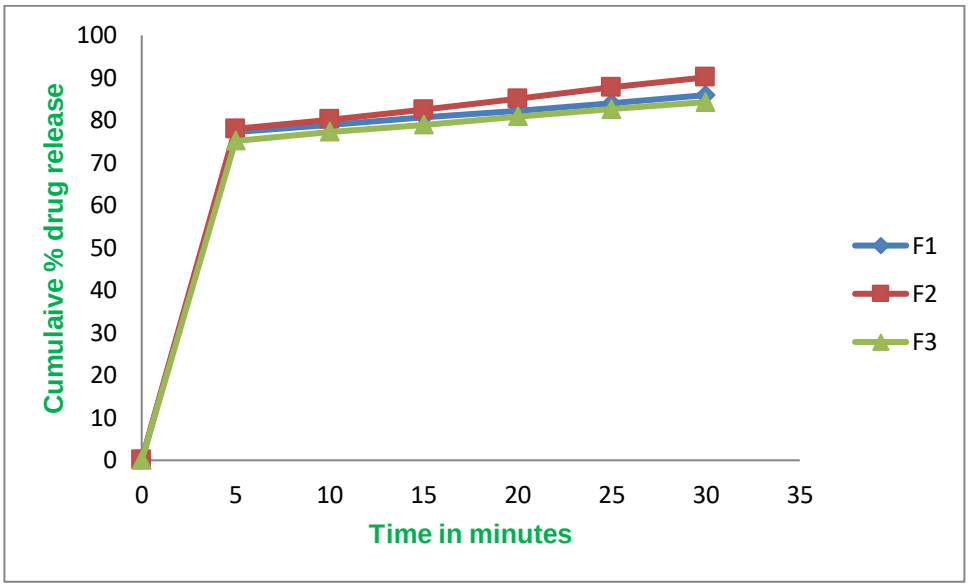


FIG.12B : *IN-VITRO* RELEASE OF LEVOCETIRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS (F4-F6)

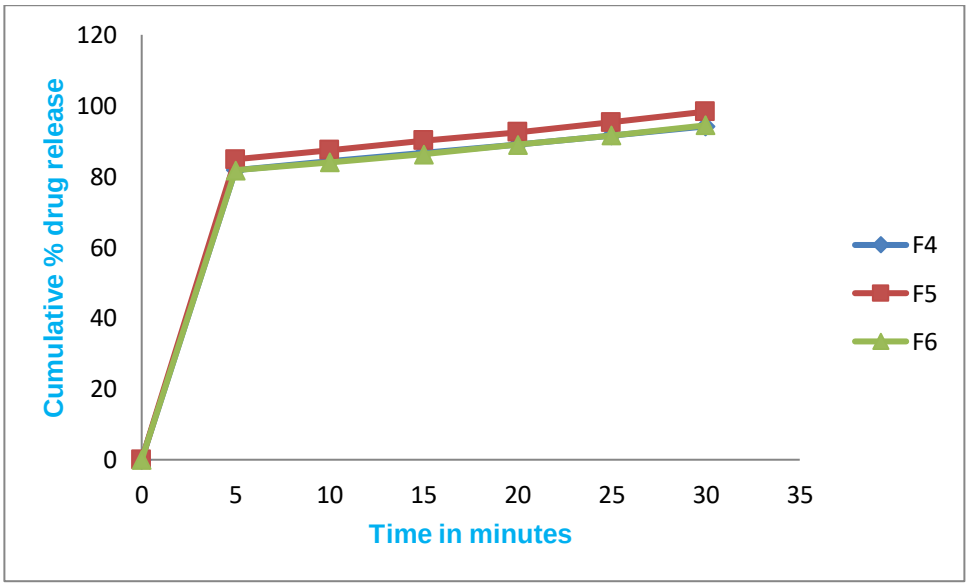


FIG.12C : *IN-VITRO* RELEASE OF LEVOCETIRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS (F7-F9)

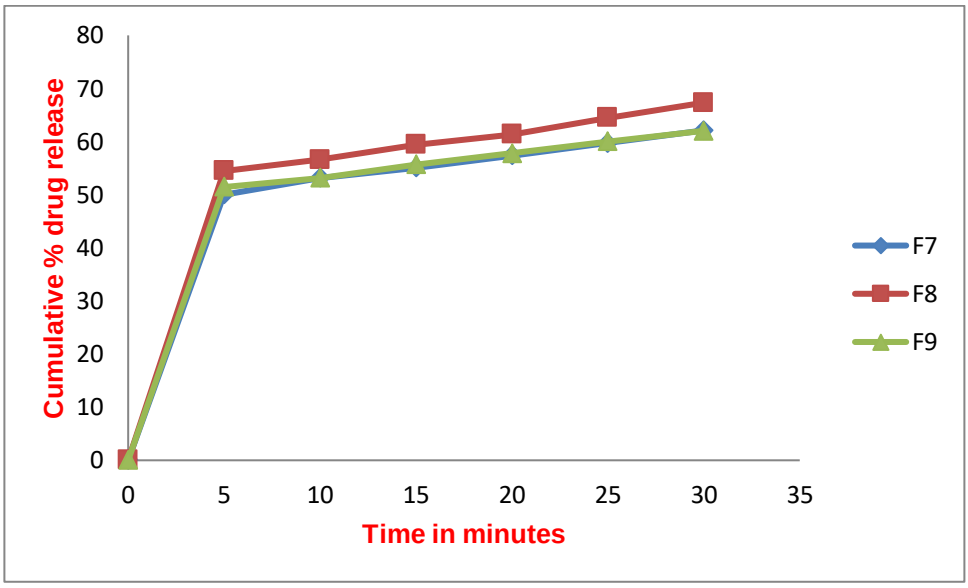


FIG.12D : *IN-VITRO* RELEASE OF LEVOCETIRIZINE HYDROCHLORIDE ORODISPERSIBLE TABLETS (F10-F12)

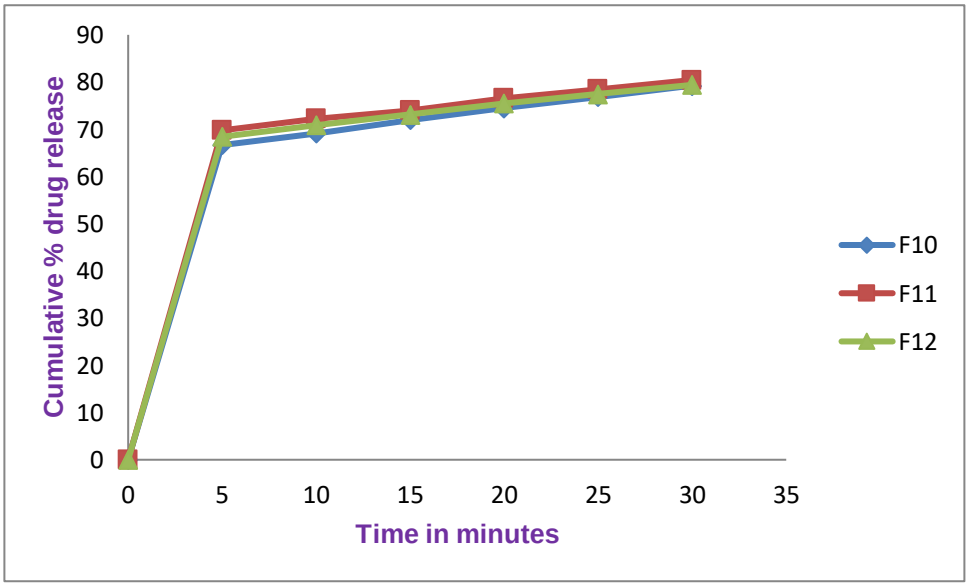


FIG.13A : COMPARISON OF *IN-VITRO* ZERO ORDER RELEASE KINETICS FOR FPRMULATION CONTAINING SODIUM STARCH GLYCOLATE

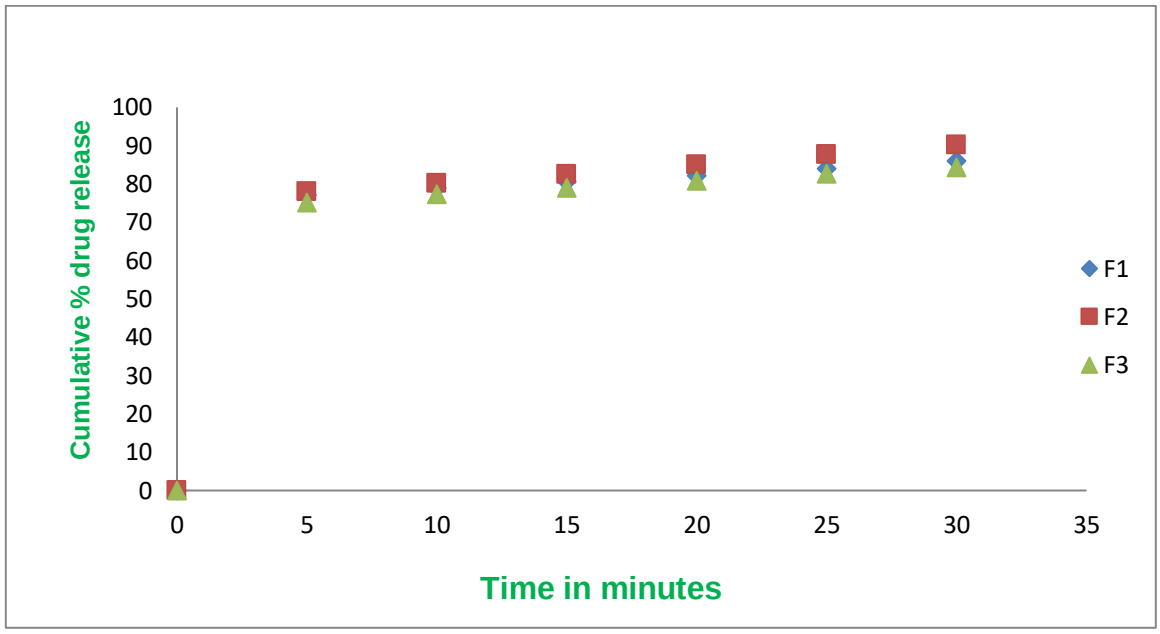


FIG.13B : COMPARISON OF *IN-VITRO* ZERO ORDER RELEASE KINETICS FOR FPRMULATION CONTAINING CROSPOVIDONE

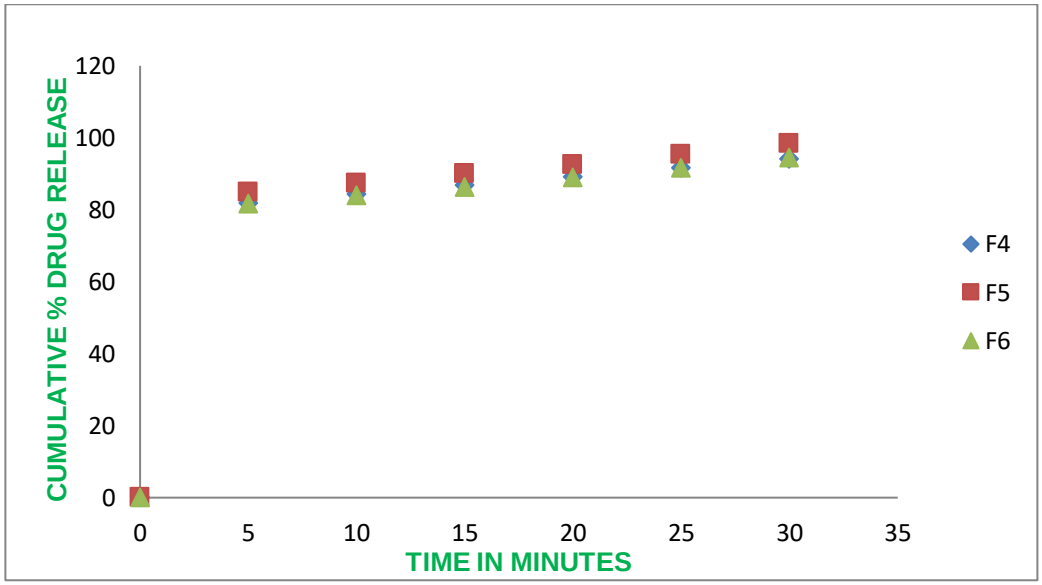


FIG.13C : COMPARISON OF *IN-VITRO* ZERO ORDER RELEASE KINETICS FOR FPRMULATION CONTAINING HIBISCUS LEAVES MUCILAGE

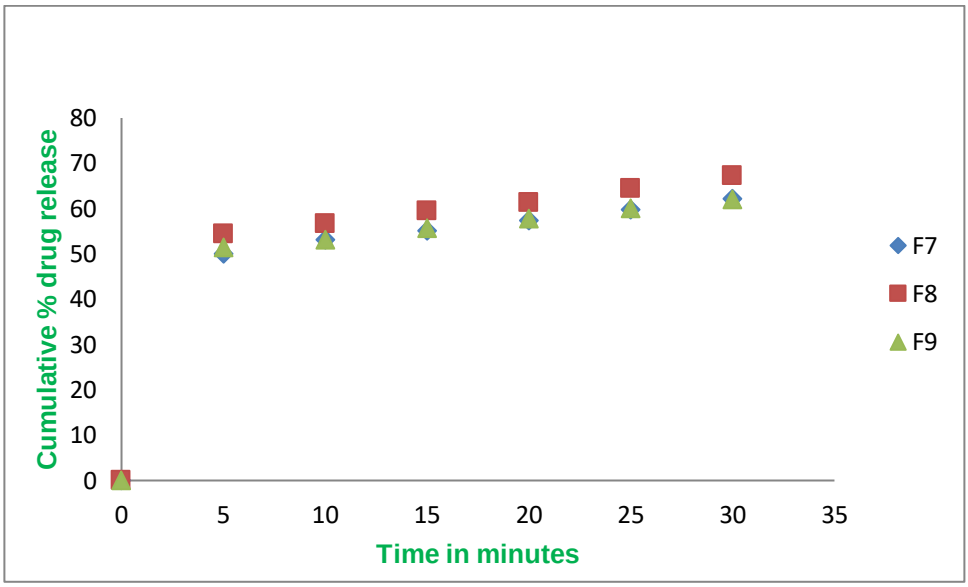


FIG.13D : COMPARISON OF *IN-VITRO* ZERO ORDER RELEASE KINETICS FOR FPRMULATION CONTAINING PLANTAGO OVATA SEED MUCILAGE

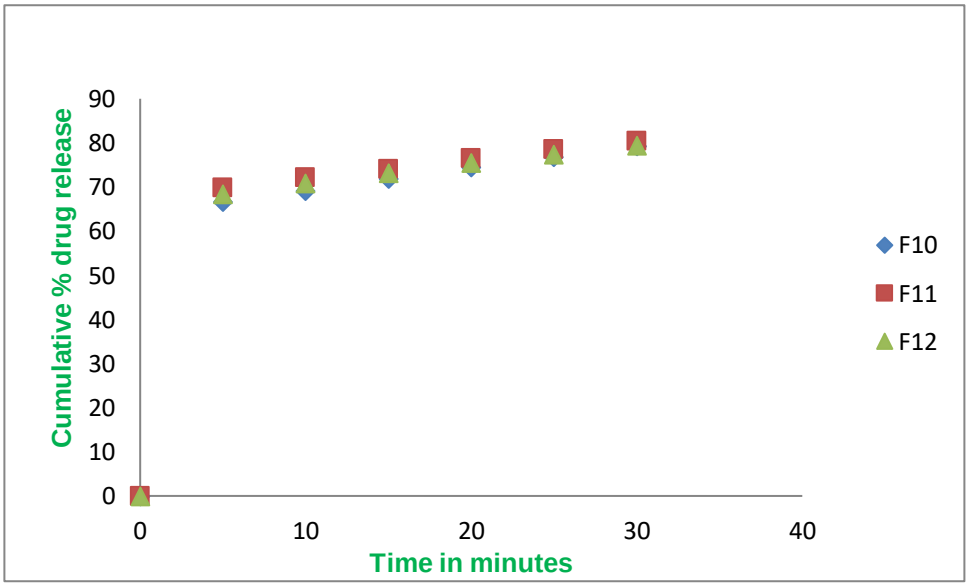


FIG.14A : COMPARISON OF *IN-VITRO* FIRST ORDER RELEASE KINETICS FOR FPRMULATION CONTAINING SODIUM STARCH GLYCOLATE

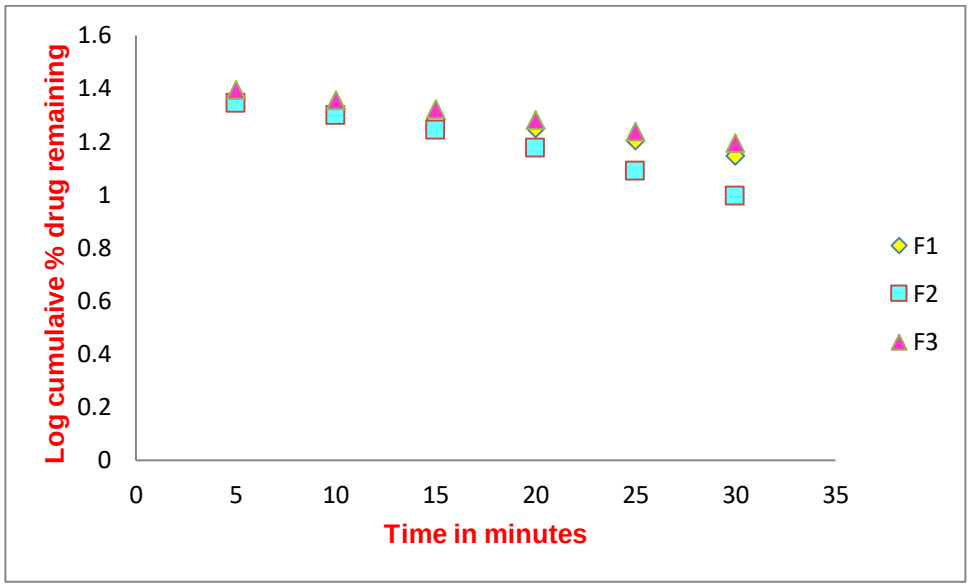


FIG.14B : COMPARISON OF *IN-VITRO* FIRST ORDER RELEASE KINETICS FOR FPRMULATION CONTAINING CROSPOVIDONE

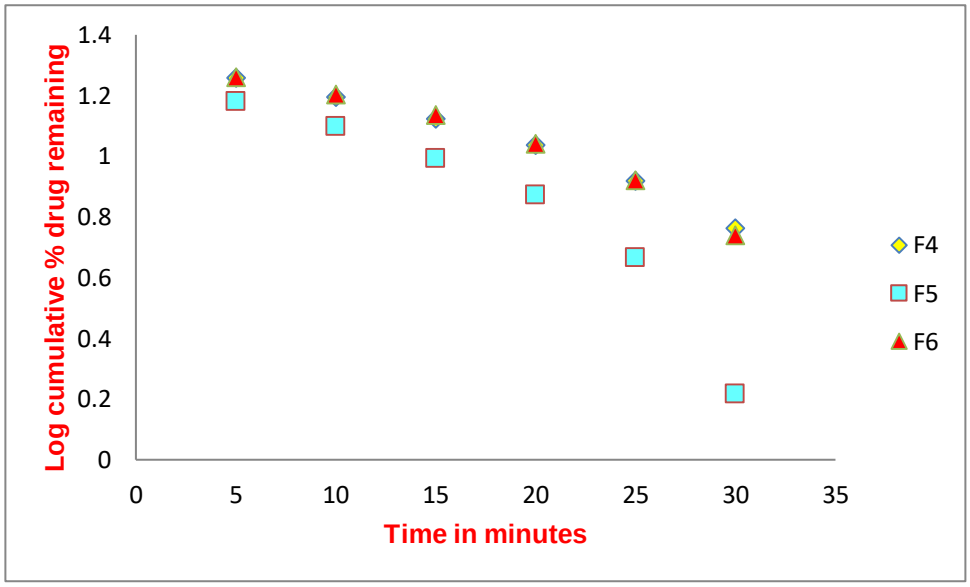


FIG.14C : COMPARISON OF *IN-VITRO* FIRST ORDER RELEASE KINETICS FOR FPRMULATION CONTAINING HIBISCUS LEAVES MUCILAGE

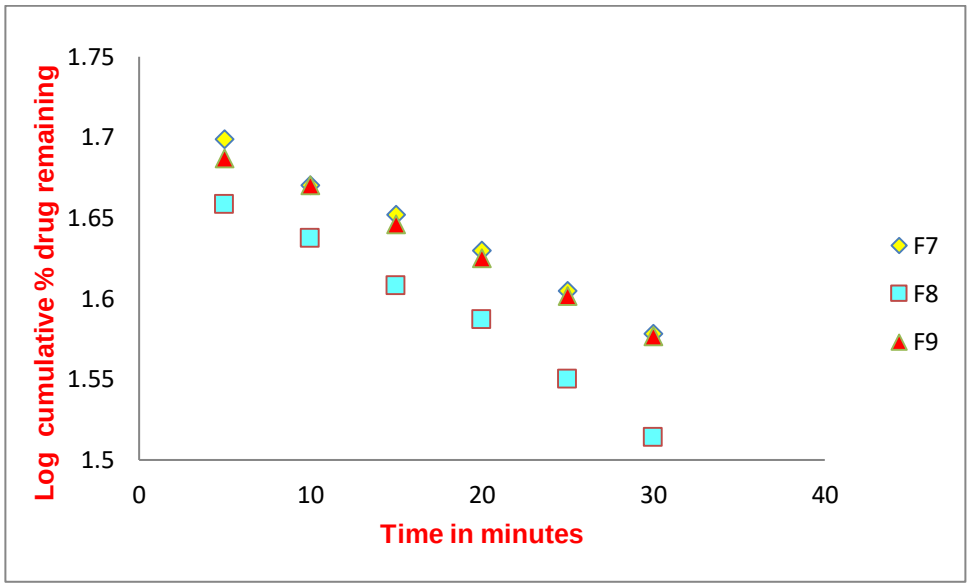


FIG.14D : COMPARISON OF *IN-VITRO* FIRST ORDER RELEASE KINETICS FOR FPRMULATION CONTAINING PLANTAGO OVATA SEED MUCILAGE

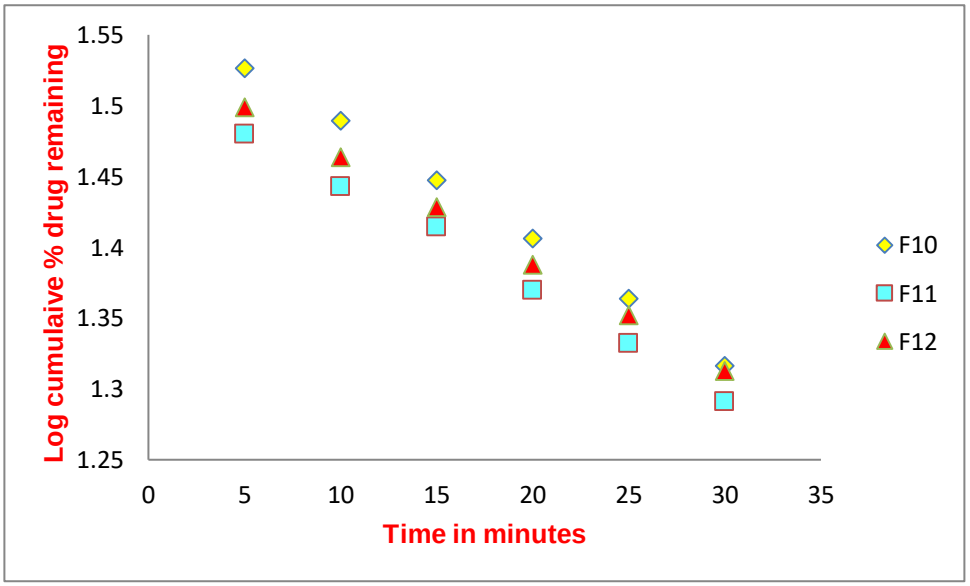


FIG.15A : COMPARISON OF *IN-VITRO* HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING SODIUM STARCH GLYCOLATE

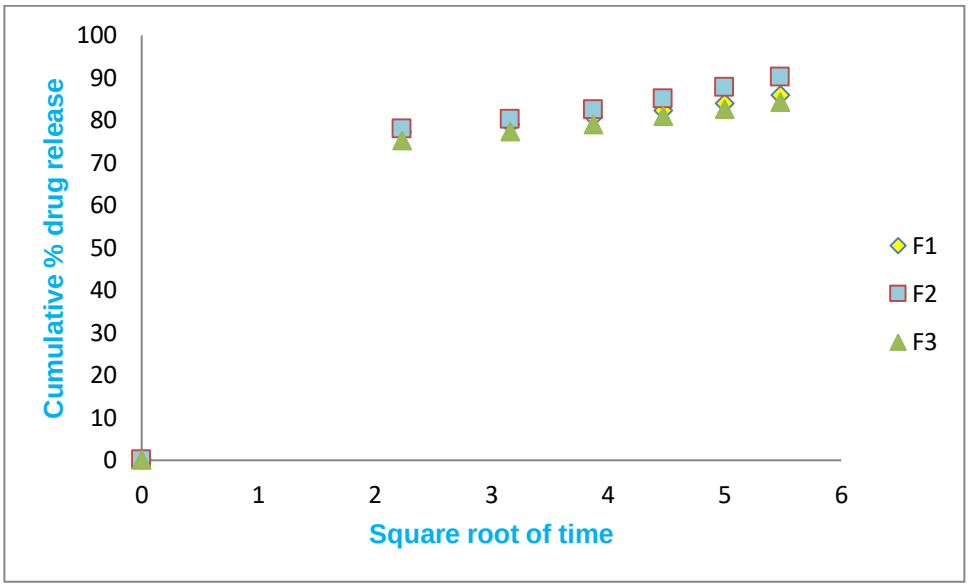


FIG.15B : COMPARISON OF *IN-VITRO* HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING CROSPOVIDON

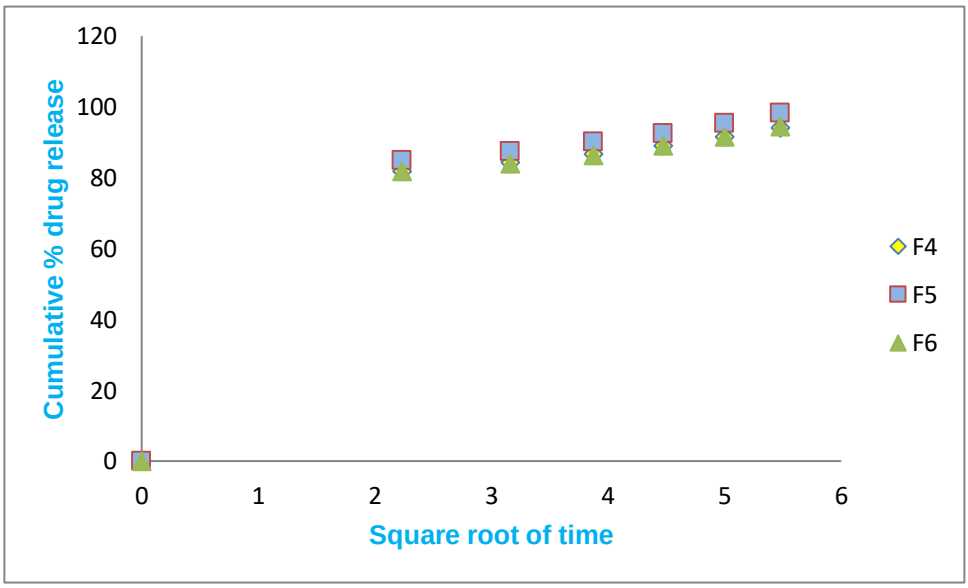


FIG.15C : COMPARISON OF *IN-VITRO* HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING HIBISCUS LEAVES MUCILAGE

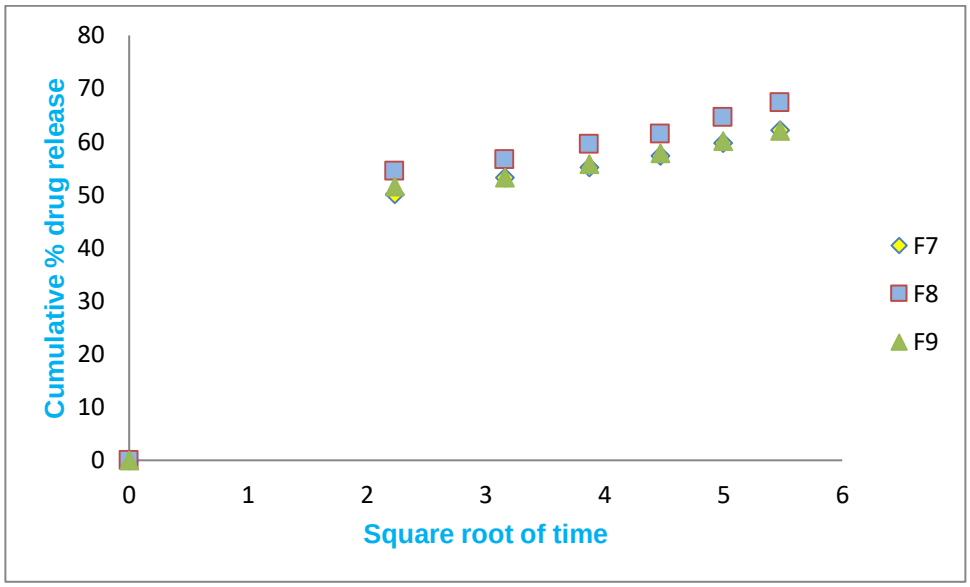


FIG.15D : COMPARISON OF *IN-VITRO* HIGUCHI MODEL RELEASE KINETICS OF FORMULATION CONTAINING PLANTAGO OVATA SEED MUCILAGE

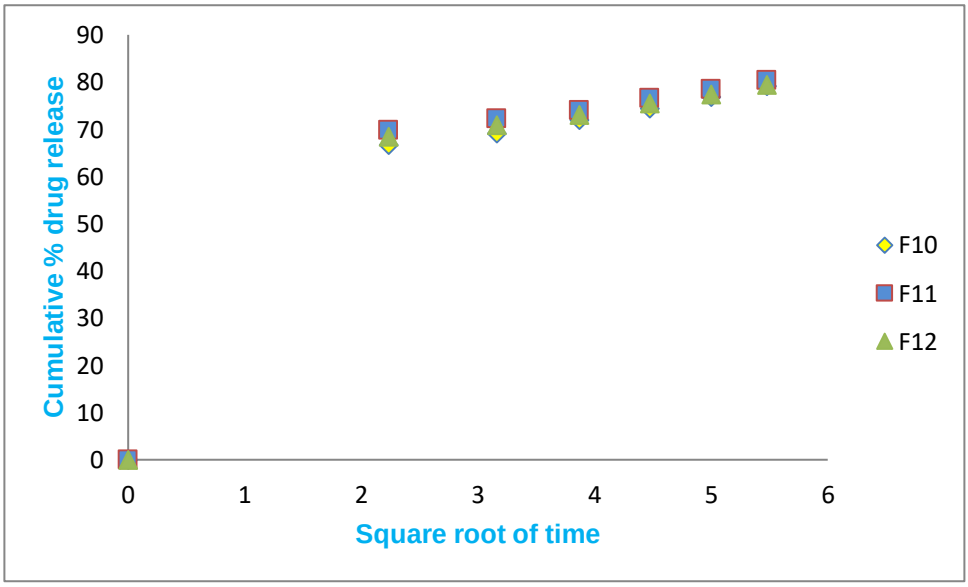


FIG.16A : COMPARISON OF *IN-VITRO* KORSMEYER PEPPAS MODEL RELEASE KINETIC OF FORMULATION CONTAINING SODIUM STARCH GLYCOLATE

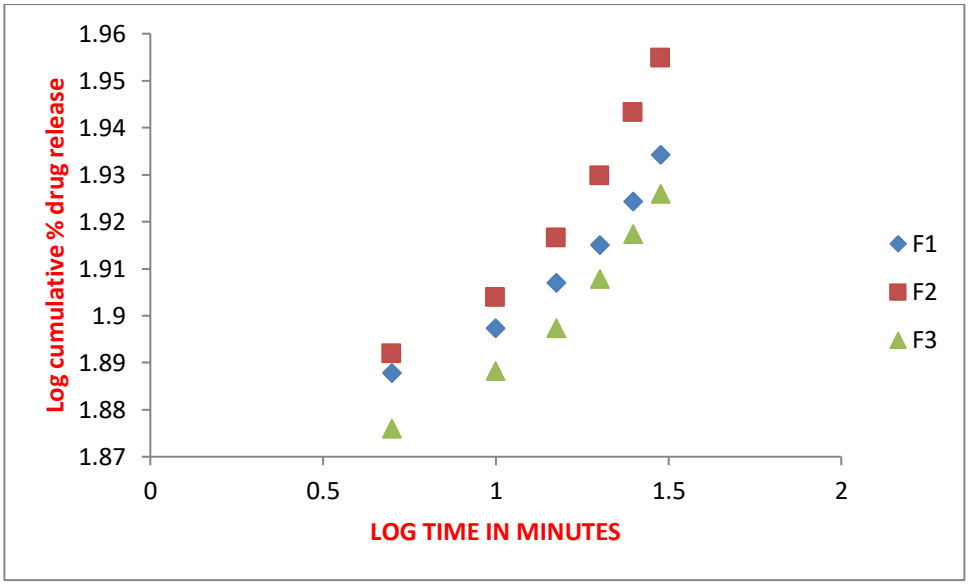


FIG.16B : COMPARISON OF *IN-VITRO* KORSMEYER PEPPAS MODEL RELEASE KINETIC OF FORMULATION CONTAINING CROSPOVIDONE

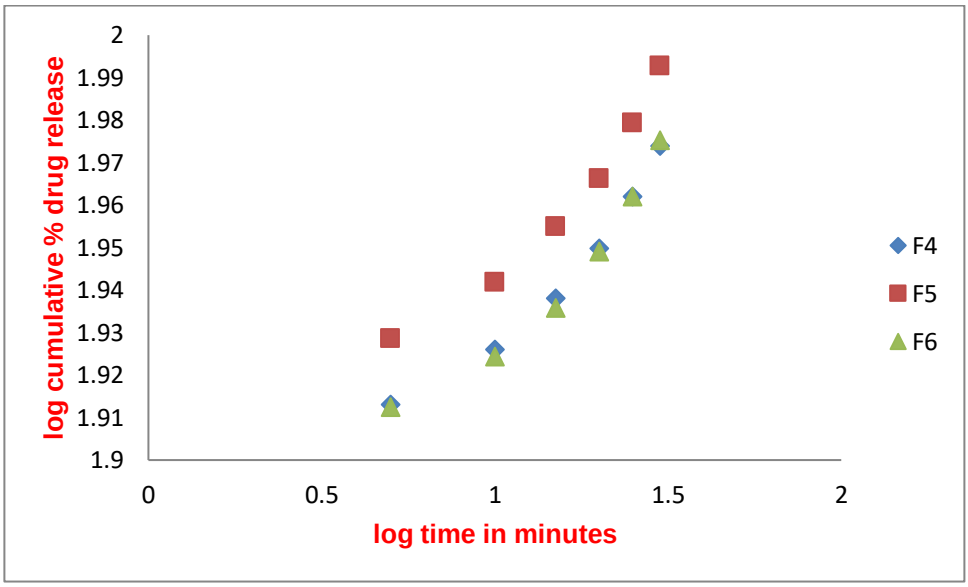


FIG.16C : COMPARISON OF *IN-VITRO* KORSMEYER PEPPAS MODEL RELEASEKINETIC OF FORMULATION CONTAINING HIBISCUS LEAVES MUCILAGE

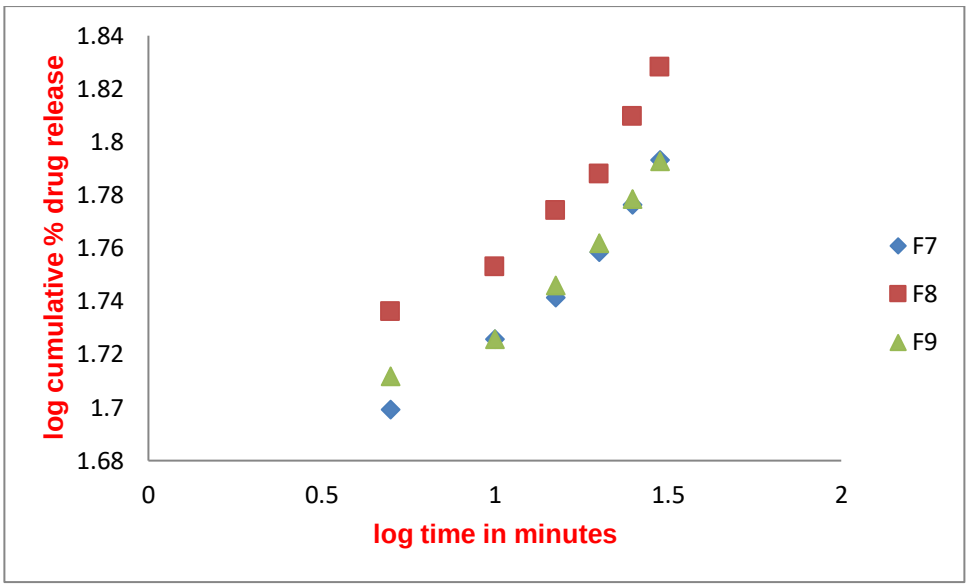


FIG.16D : COMPARISON OF *IN-VITRO* KORSMEYER PEPPAS MODEL RELEASE KINETIC OF FORMULATION CONTAINING PLANTAGO OVATA SEED MUCILAGE

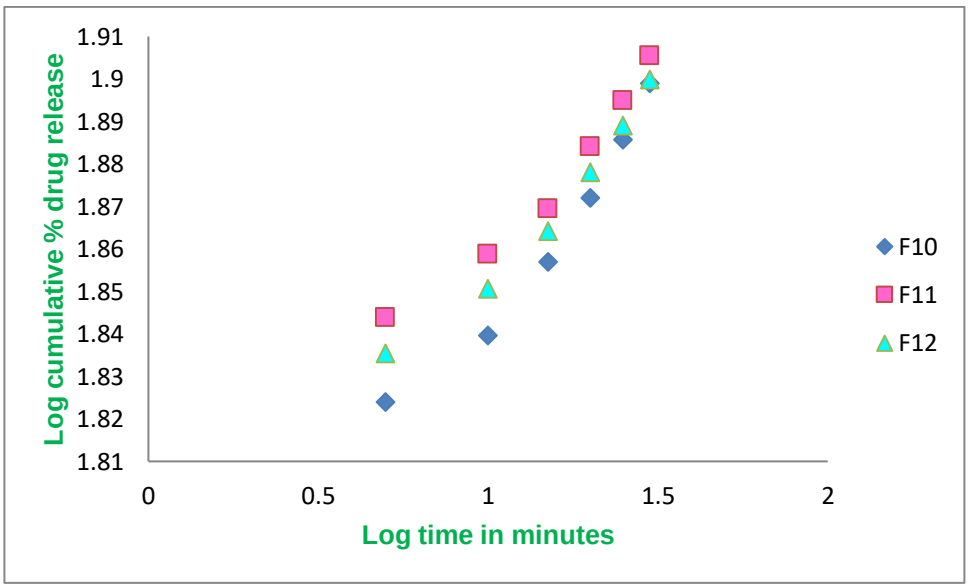


FIG.17A : COMPARISON OF *IN-VITRO* HIXSON CROWELL MODEL RELEASE KINETICS FOR FORMULATIONS CONTAINING SODIUM STARCH GLYCOLATE

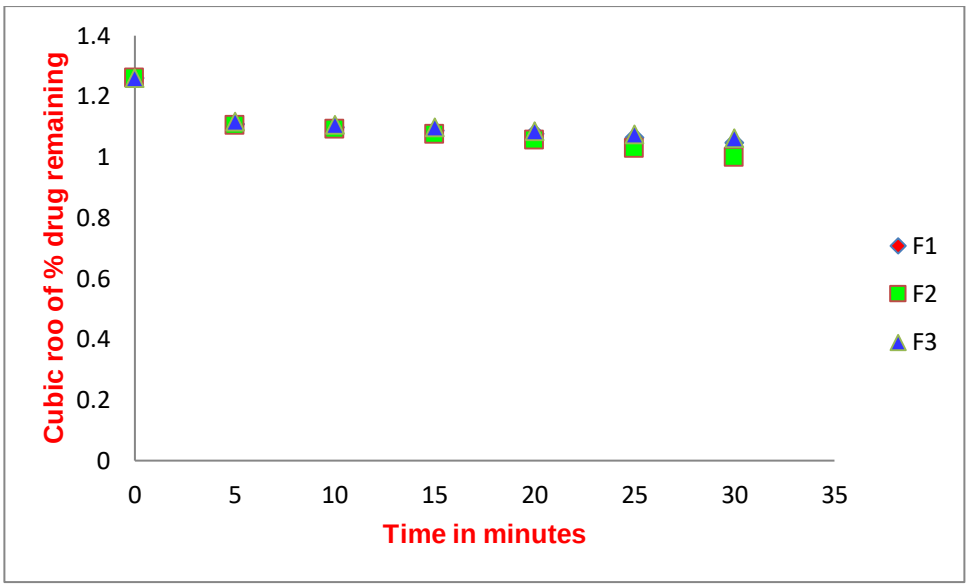


FIG.17B : COMPARISON OF *IN-VITRO* HIXSON CROWELL MODEL RELEASE KINETICS FOR FORMULATIONS CONTAINING CROSPOVIDONE

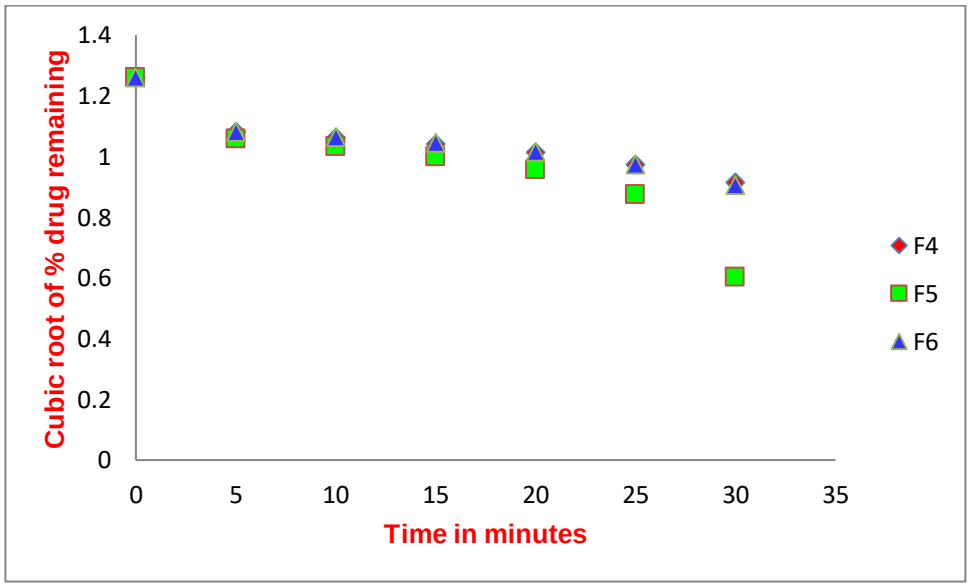


FIG.17C : COMPARISON OF *IN-VITRO* HIXSON CROWELL MODEL RELEASE KINETICS FOR FORMULATIONS CONTAINING HIBISCUS LEAVES MUCILAGE

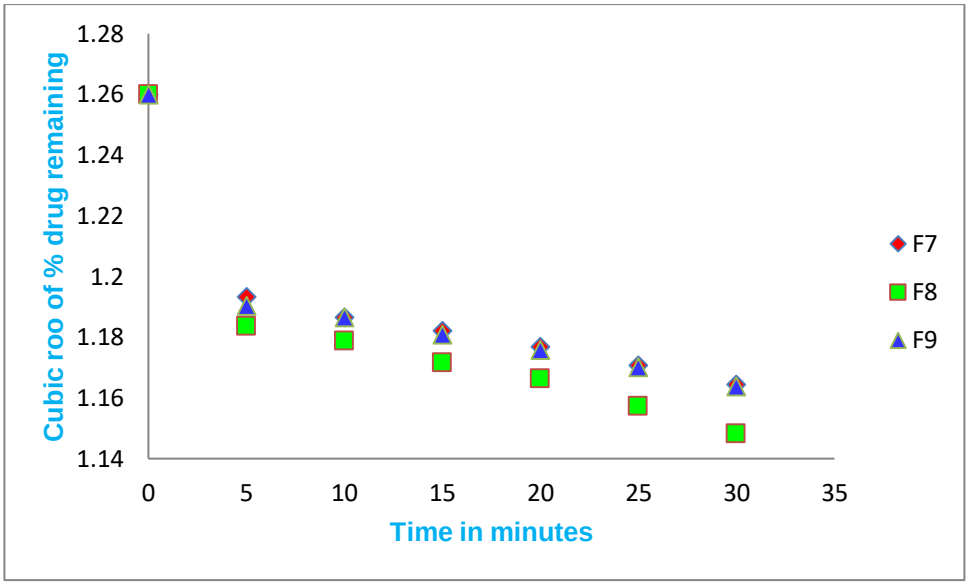
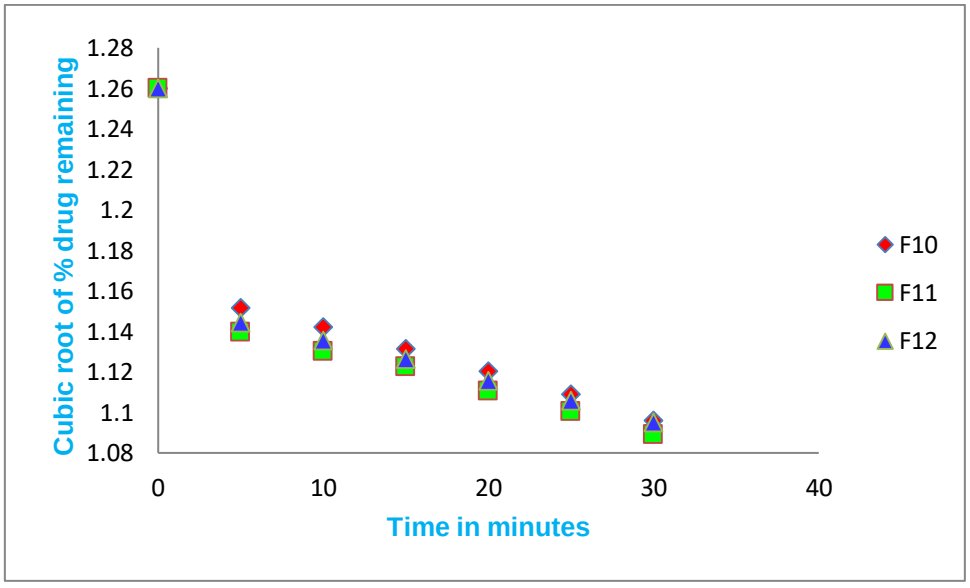


FIG.17D : COMPARISON OF *IN-VITRO* HIXSON CROWELL MODEL RELEASE KINETICS FOR FORMULATIONS CONTAINING PLANTAGO OVATA SEED MUCILAGE



CHAPTER – X

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

- Aim of this study was to prepare Levocetirizine Hydrochloride orodispersible tablets using different synthetic and natural superdisintegrants and to compare the effect of different superdisintegrants on the release profile of the formulation.
- The results of Fourier Transmission Infra- Red spectroscopy confirmed that the drug and excipients were compatible with each other and were devoid of interactions.
- The results of precompression studies like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio reveals that the prepared powder blends of formulations possess good flow properties with synthetic superdisintegrants and passable flow property with natural superdisintegrants.
- The orodispersible tablets are prepared by direct compression technique using superdisinegrants in different concentration (2.5 %, 5% and 7.5%), mannitol as bulking material, MCC as a binder, saccharin sodium as a sweetening agent .
- The prepared tablets were subjected to post compression evaluations and the results indicated that the hardness, thickness, wetting time and water absorption ratio of the tablets prepared from the synthetic superdisintegrant (Crospovidone) were better when compared with the other formulations. All the tablets were of uniform size and shape with

good resistance against mechanical damage.

- The tablets of all formulations contains uniform amount of drug, which ensures content uniformity for tablets of all formulations.
- The tablets were within the limits of weight variation test, which in turn indicate uniform distribution of contents of the powder blends of each formulations.
- The friability of all the tablets was found to be < 1%, which indicates the good mechanical resistance.
- The tablets of best formulations F5 containing 5% crospovidone as superdisintegrant was found to have minimum wetting time and maximum water absorption ratio which is the desired characteristic of orodispersible tablets, which enabled faster disintegration of tablets.
- Among all the formulations, the best formulation was selected on the basis of lowest disintegration time, rapid drug release profile, higher water absorption ratio, short wetting time. Formulation F5 showed lowest disintegration time of 39.7 seconds, faster drug release rate of 98.31% in 30 minutes, comparatively high water absorption ratio of 84.87%, short wetting time of 47.3 seconds and minimum chemicals composition. In those parameter would drive the F5 formulation as a best comparatively.

CONCLUSION

Orodispersible tablets of Levocetrizine Hydrochloride tabltes prepared by direct compression technique containing synthetic superdisintegrants crospovidone (5%) was found to be better disintegration property because of its combination effect of swelling and wicking and showed best *in-vitro* dissolution profile than the formulations containing natural superdisintegrants (hibiscus leaves dried mucilage and plantago ovata seed mucilage). Hence, it can be concluded that using a crospovidone can be used as a first choice fof superdisintegrant for the formation of orodispersible tablets.

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Thank
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